MacroModel 9.1

Quick Start Guide

Schrödinger Press

Revision A, May 2006

Contents

Document Conventions

In addition to the use of italics for names of documents, the font conventions that are used in this document are summarized in the table below.

Table 3.1.

Font	Example	Use
Sans serif	Project Table	Names of GUI features, such as panels, menus, menu items, buttons, and labels
Monospace	`$SCHRODINGER/maestro`	File names, directory names, commands, environment variables, and screen output
Italic	*filename*	Text that the user must replace with a value
Sans serif uppercase	CTRL+H	Keyboard keys

In descriptions of command syntax, the following UNIX conventions are used: braces `{ }` enclose a choice of required items, square brackets `[ ]` enclose optional items, and the bar symbol `|` separates items in a list from which one item must be chosen. Lines of command syntax that wrap should be interpreted as a single command.

In this document, to *type* text means to type the required text in the specified location, and to *enter* text means to type the required text, then press the ENTER key.

References to literature sources are given in square brackets, like this: [10].

MacroModel Overview

This manual introduces you to MacroModel and Maestro, and contains exercises designed to help you learn the basic tasks for preparing and initiating MacroModel calculations from Maestro. For more information about a particular feature, see the *MacroModel User Manual*. To learn more about the command line MacroModel and MacroModel operation codes, see the *MacroModel Reference Manual*. For more information on using Maestro, see the Maestro online help or the *Maestro User Manual*.

1.1 Introduction to MacroModel

MacroModel 9.1 is a general purpose, force-field-based molecular modeling program with applicability to a wide range of chemical systems. MacroModel provides the researcher multiple advanced methods to aid in the understanding of chemical structure, energetics, and dynamics. A large selection of force fields is included, along with the latest technical advances introduced into OPLS-AA. Numerous minimization methods are available, enabling geometry optimizations for a broad selection of structural classes. A wide range of methods are available for conformational searching, which allows the researcher to efficiently sample the potential energy surface for low-energy structures, including entire proteins. Solvation effects can be accounted for using the efficient continuum solvation model in MacroModel. Additional advanced features include molecular dynamics simulations, free-energy perturbation simulations, and pure- and mixed-ensemble sampling methods. MacroModel 9.1 contains significant new features and performance enhancements, which reflect a commitment to provide the latest advancements in computational science.

1.2 MacroModel and Maestro Interaction

MacroModel runs energy calculations as independent batch mode tasks and consequently does not tie up Maestro with lengthy computations. To provide interaction with the MacroModel tasks, Maestro monitors the tasks so that both numerical and structural information may be viewed while the energetic tasks are running. Such monitoring is the default mode of operation for newly started energetic tasks, although monitoring can be discontinued and reestablished at any later time. Thus, users may initiate several MacroModel tasks, disconnect from them, carry out graphical modeling operations, and periodically reconnect to and examine the progress of each energetic task. See the *Maestro User Manual* for details.

1.3 Calculation Preparation and Submission

MacroModel calculations can be prepared and launched either from the Maestro GUI or from the command line. An overview of job submission from Maestro is provided below.

1.3.1 Starting Jobs From Maestro

Separate panels are available in Maestro for current energy, energy minimization, dihedral driving, conformational search, ligand torsion search, multiple minimization, dynamics, MC/SD, MINTA, eMBrAcE, and redundant conformer elimination calculations. XCluster calculations may also be set up and initiated from Maestro. To set up a calculation, display the relevant panel, adjust the settings as desired, and click Start. Alternatively, you can click Write to write out only the structure and command files you would need to launch the job later from the command line. For more information about launching jobs from the command line, see Chapter 4 of the *MacroModel User Manual*.

1.3.2 Starting Jobs From the Command Line

Some types of MacroModel calculations cannot be prepared or submitted from Maestro. See the *MacroModel User Manual* for details. For these jobs, you will need to manually create the necessary command file, which provides MacroModel with the instructions it needs to perform the intended calculation. When doing this, you may prefer to use a Maestro-generated command file as a template, and adjust the file as needed. The *MacroModel Reference Manual* contains detailed information about all of the MacroModel commands and operational codes. In addition, the *MacroModel User Manual* describes many typical examples of various types of MacroModel calculations, and the corresponding command files may be available in the following directory:

`$SCHRODINGER/macromodel-v`*version*`/samples/Examples`

Because all jobs are now handled by the Schrödinger Job Control facility, MacroModel jobs can be monitored from Maestro, even jobs launched from the command line.

Introduction to Maestro

Maestro is the graphical user interface for all of Schrödinger's products: CombiGlide™, Epik™, Glide™, Impact™, Jaguar™, Liaison™, LigPrep™, MacroModel®, Phase™, Prime™, QikProp™, QSite™, and Strike™. It contains tools for building, displaying, and manipulating chemical structures; for organizing, loading, and storing these structures and associated data; and for setting up, monitoring, and visualizing the results of calculations on these structures. This chapter provides a brief introduction to Maestro and some of its capabilities. For more information on any of the topics in this chapter, see the *Maestro User Manual*.

2.1 General Interface Behavior

Most Maestro panels are amodal: more than one panel can be open at a time, and a panel need not be closed for an action to be carried out. Each Maestro panel has a Close button so you can hide the panel from view.

Maestro supports the mouse functions common to many graphical user interfaces. The left button is used for choosing menu items, clicking buttons, and selecting objects by clicking or dragging. This button is also used for resizing and moving panels. The right button displays a shortcut menu. Other common mouse functions are supported, such as using the mouse in combination with the SHIFT or CTRL keys to select a range of items and select or deselect a single item without affecting other items.

In addition, the mouse buttons are used for special functions described later in this chapter. These functions assume that you have a three-button mouse. If you have a two-button mouse, ensure that it is configured for three-button mouse simulation (the middle mouse button is simulated by pressing or holding down both buttons simultaneously).

2.2 Starting Maestro

Before starting Maestro, you must first set the `SCHRODINGER` environment variable to point to the installation directory. To set this variable, enter the following command at a shell prompt:

csh/tcsh: `setenv SCHRODINGER` *installation-directory*

bash/ksh: `export SCHRODINGER=`*installation-directory*

You might also need to set the `DISPLAY` environment variable, if it is not set automatically when you log in. To determine if you need to set this variable, enter the command:

```
echo $DISPLAY
```

If the response is a blank line, set the variable by entering the following command:

csh/tcsh: `setenv DISPLAY` *display-machine-name*`:0.0`

bash/ksh: `export DISPLAY=`*display-machine-name*`:0.0`

After you set the `SCHRODINGER` and `DISPLAY` environment variables, you can start Maestro using the command:

`$SCHRODINGER/maestro` *options*

If you add the `$SCHRODINGER` directory to your path, you only need to enter the command `maestro`. Options for this command are given in Section 2.1 of the *Maestro User Manual*.

The directory from which you started Maestro is Maestro's current working directory, and all data files are written to and read from this directory unless otherwise specified (see Section 2.8 on page 25). You can change directories by entering the following command in the command input area (see page 6) of the main window:

`cd` *directory-name*

where *directory-name* is either a full path or a relative path.

2.3 The Maestro Main Window

The Maestro main window is shown in Figure 2.1 on page 5. The main window components are listed below.

The following components are always visible:

- **Title bar**—displays the Maestro version, the project name (if there is one) and the current working directory.
- **Auto-Help**—automatically displays context-sensitive help.
- **Menu bar**—provides access to panels.
- **Workspace**—displays molecular structures and other 3D graphical objects.

The following components can be displayed or hidden by choosing the component from the Display menu. Your choice of which main window components are displayed is persistent between Maestro sessions.

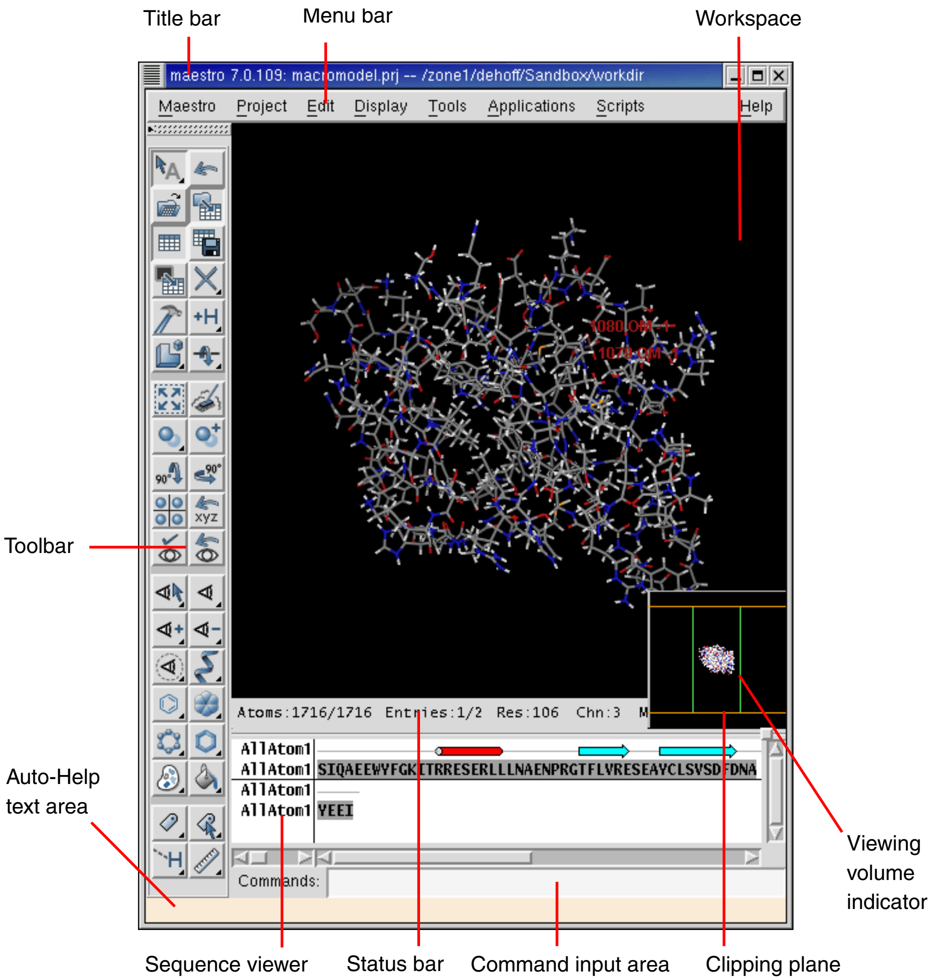


Figure 2.1. The Maestro main window.

- **Toolbar**—contains buttons for many common tasks and provides tools for displaying and manipulating structures, as well as organizing the Workspace.
- **Status bar**—displays information about a particular atom, or about structures in the Workspace, depending on where the pointer pauses (see Section 2.5 of the *Maestro User Manual* for details):
  - **Atom**—displays the chain, residue number, element, PDB atom name, formal charge, and title or entry name (this last field is set by choosing Preferences from the Maestro menu and selecting the Feedback folder).

  - **Workspace**—displays the number of atoms, entries, residues, chains, and molecules in the Workspace.
- **Clipping planes window**—displays a small, top view of the Workspace and shows the clipping planes and viewing volume indicators.
- **Sequence viewer**—shows the sequences for proteins displayed in the Workspace. See Section 2.6 of the *Maestro User Manual* for details.
- **Command input area**—provides a place to enter Maestro commands.

When a distinction between components in the main window and those in other panels is needed, the term *main* is applied to the main window components (e.g., main toolbar).

You can expand the Workspace to occupy the full screen, by pressing CTRL+=. All other components and panels are hidden. To return to the previous display, press CTRL+= again.

2.3.1 The Menu Bar

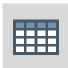
The menus on the main menu bar provide access to panels, allow you to execute commands, and control the appearance of the Workspace. The main menus are as follows:

- Maestro—save or print images in the Workspace, execute system commands, save or load a panel layout, set preferences, set up Maestro command aliases, and quit Maestro.
- Project—open and close projects, import and export structures, make a snapshot, and annotate a project. These actions can also be performed from the Project Table panel. For more information, see Section 2.4 on page 11.
- Edit—undo actions, build and modify structures, define command scripts and macros, and find atoms in the Workspace.
- Display—control the display of the contents of the Workspace, arrange panels, and display or hide main window components.
- Tools—group atoms; measure, align, and superimpose structures; and view and visualize data.
- Applications—set up, submit, and monitor jobs for Schrödinger's computational programs. Some products have a submenu from which you can choose the task to be performed.
- Scripts—manage and install Python scripts that come with the distribution and scripts that you create yourself. (See Chapter 13 of the *Maestro User Manual* for details.)
- Help—open the Help panel, the PDF documentation index, or information panels; run a demonstration; and display or hide Balloon Help (tooltips).

2.3.2 The Toolbar

The main toolbar contains three kinds of buttons for performing common tasks:

Action—Perform a simple task, like clearing the Workspace.



Display—Open or close a panel or open a dialog box, such as the Project Table panel.

Menu—Display a *button menu*. These buttons have a triangle in the lower right corner.

There are four types of items on button menus, and all four types can be on the same menu (see Figure 2.2):

- **Action**—Perform an action immediately.
- **Display**—Open a panel or dialog box.
- **Object types for selection**—Choose Atoms, Bonds, Residues, Chains, Molecules, or Entries, then click on an atom in the Workspace to perform the action on all the atoms in that structural unit.

  The object type is marked on the menu with a red diamond and the button is indented to indicate the action to be performed.
- **Other setting**—Set a state, choose an attribute, or choose a parameter and click on atoms in the Workspace to display or change that parameter.

The toolbar buttons are described below. Some descriptions refer to features not described in this chapter. See the *Maestro User Manual* for a fuller description of these features.

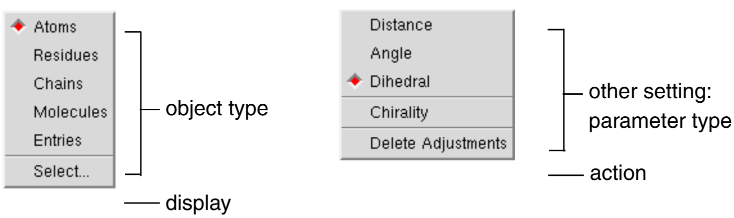


Figure 2.2. The Workspace selection ***button menu and the*** Adjust distances, angles or dihedrals ***button menu.***

Workspace selection
– Choose an object type for selecting
– Open the Atom Selection dialog box

Undo/Redo
Undo or redo the last action. Performs the same function as the Undo item on the Edit menu, and changes to an arrow pointing in the opposite direction when an Undo has been performed, indicating that its next action is Redo.

Open a project
Open the Open Project dialog box.

Import structures
Open the Import panel.

Open/Close Project Table
Open the Project Table panel or close it if it is open.

Save as
Open the Save Project As dialog box, to save the project with a new name.

Create entry from Workspace
Open a dialog box in which you can create an entry in the current project using the contents of the Workspace.

Delete
– Choose an object type for deletion
– Delete hydrogens and waters
– Open the Atom Selection dialog box
– Delete other items associated with the structures in the Workspace
– Click to select atoms to delete
– Double-click to delete all atoms

Open/Close Build panel
Open the Build panel or close it if it is open.

Add hydrogens
– Choose an object type for applying a hydrogen treatment
– Open the Atom Selection dialog box
– Click to select atoms to treat
– Double-click to apply to all atoms

Local transformation
– Choose an object type for transforming
– Click to select atoms to transform
– Open the Advanced Transformations panel

Adjust distances, angles or dihedrals
– Choose a parameter for adjusting
– Delete adjustments

Fit to screen
Scale the displayed structure to fit into the Workspace and reset the center of rotation.

Clear Workspace
Clear all atoms from the Workspace.

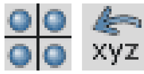
Set fog display state
Choose a fog state. Automatic means fog is on when there are more than 40 atoms in the Workspace, otherwise it is off.

Enhance depth cues
Optimize fogging and other depth cues based on what is in the Workspace.

Rotate around X axis by 90 degrees
Rotate the Workspace contents around the X axis by 90 degrees.

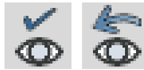
Rotate around Y axis by 90 degrees
Rotate the Workspace contents around the Y axis by 90 degrees.

Tile entries
Arrange entries in a rectangular grid in the Workspace.



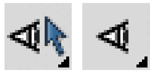
Reset Workspace
Reset the rotation, translation, and zoom of the Workspace to the default state.

Save view
Save the current view of the Workspace: orientation, location, and zoom.



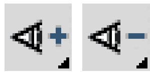
Restore view
Restore the last saved view of the Workspace: orientation, location, and zoom.

Display only selected atoms
– Choose an object type for displaying
– Click to select atoms to display
– Double-click to display all atoms



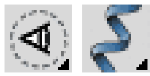
Display only
– Choose a predefined atom category
– Open the Atom Selection dialog box

Also display
– Choose a predefined atom category
– Open the Atom Selection dialog box



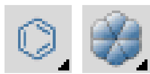
Undisplay
– Choose a predefined atom category
– Open the Atom Selection dialog box

Display residues within N angstroms of currently displayed atoms
– Choose a radius
– Open a dialog box to set a value



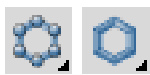
Show, hide, or color ribbons
– Choose to show or hide ribbons
– Choose a color scheme for coloring ribbons

Draw bonds in wire
– Choose an object type for drawing bonds in wire representation
– Open the Atom Selection dialog box
– Click to select atoms for representation
– Double-click to apply to all atoms



Draw atoms in CPK
– Choose an object type for drawing bonds in CPK representation
– Open the Atom Selection dialog box
– Click to select atoms for representation
– Double-click to apply to all atoms

Draw atoms in Ball & Stick
– Choose an object type for drawing bonds in Ball & Stick representation
– Open the Atom Selection dialog box
– Click to select atoms for representation
– Double-click to apply to all atoms

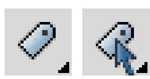


Draw bonds in tube
– Choose an object type for drawing bonds in tube representation
– Open the Atom Selection dialog box
– Click to select atoms for representation
– Double-click to apply to all atoms

Color all atoms by scheme
Choose a predefined color scheme.

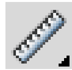
Color residue by constant color
– Choose a color for applying to residues
– Click to select residues to color
– Double-click to color all atoms

Label atoms
– Choose a predefined label type
– Delete labels



Label picked atoms
– Choose an object type for labeling atoms
– Open the Atom Selection dialog box
– Open the Atom Labels panel at the Composition folder
– Delete labels
– Click to select atoms to label
– Double-click to label all atoms

Display H-bonds
– Choose bond type:
intra—displays H-bonds within the selected molecule
inter—displays H-bonds between the selected molecule and all other atoms.
– Delete H-bonds
– Click to select molecule



Measure distances, angles or dihedrals
– Choose a parameter for displaying measurements
– Delete measurements
– Click to select atoms for measurement

2.3.3 Mouse Functions in the Workspace

The left mouse button is used for selecting objects. You can either click on a single atom or bond, or you can drag to select multiple objects. The right mouse button opens shortcut menus, which are described in Section 2.7 of the *Maestro User Manual*.

The middle and right mouse buttons can be used on their own and in combination with the SHIFT and CTRL keys to perform common operations, such as rotating, translating, centering, adjusting, and zooming.

Table 2.1. Mapping of Workspace operations to mouse actions.

Mouse Button	Keyboard	Motion	Action
Left		click, drag	Select
Left	SHIFT	click, drag	Toggle the selection
Middle		drag	Rotate about X and Y axes Adjust bond, angle, or dihedral
Middle	SHIFT	drag vertically	Rotate about X axis
Middle	SHIFT	drag horizontally	Rotate about Y axis
Middle	CTRL	drag horizontally	Rotate about Z axis
Middle	SHIFT + CTRL	drag horizontally	Zoom
Right		click	Spot-center on selection
Right		click and hold	Display shortcut menu
Right		drag	Translate in the X-Y plane
Right	SHIFT	drag vertically	Translate along the X axis
Right	SHIFT	drag horizontally	Translate along the Y axis
Right	CTRL	drag horizontally	Translate along the Z axis
Middle & Right		drag horizontally	Zoom

2.3.4 Shortcut Key Combinations

Some frequently used operations have been assigned shortcut key combinations. The shortcuts available in the main window are described in Table 2.2.

Table 2.2. Shortcut keys in the Maestro main window.

Keys	Action	Equivalent Menu Choices
CTRL+B	Open Build panel	Edit > Build
CTRL+C	Create entry	Project > Create Entry From Workspace
CTRL+E	Open Command Script Editor panel	Edit > Command Script Editor
CTRL+F	Open Find Atoms panel	Edit > Find
CTRL+H	Open Help panel	Help > Help
CTRL+I	Open Import panel	Project > Import Structures
CTRL+M	Open Measurements panel	Tools > Measurements
CTRL+N	Create new project	Project > New
CTRL+O	Open project	Project > Open
CTRL+P	Print	Maestro > Print
CTRL+Q	Quit	Maestro > Quit
CTRL+S	Open Sets panel	Tools > Sets
CTRL+T	Open Project Table panel	Project > Show Table
CTRL+W	Close project	Project > Close
CTRL+Z	Undo/Redo last command	Edit > Undo/Redo
CTRL+=	Enter and exit full screen mode (Workspace occupies full screen)	None

2.4 Maestro Projects

All the work you do in Maestro is done within a *project*. A project consists of a set of *entries*, each of which contains one or more chemical structures and their associated data. In any Maestro session, there can be only one Maestro project open. If you do not specify a project when you start Maestro, a *scratch* project is created. You can work in a scratch project without saving it, but you must save it in order to use it in future sessions. When you save or close a project, all the view transformations (rotation, translation, and zoom) are saved with it. When you close a project, a new scratch project is automatically created.

Likewise, if there is no entry displayed in the Workspace, Maestro creates a *scratch* entry. Structures that you build in the Workspace constitute a scratch entry until you save the structures as project entries. The scratch entry is not saved with the project unless you explicitly add it to the project. However, you can use a scratch entry as input for some calculations.

To add a scratch entry to a project, do one of the following:

- Click the Create entry from Workspace button:

- Choose Create Entry from Workspace from the Project menu.
- Press CTRL+C.

In the dialog box, enter a name and a title for the entry. The entry name is used internally to identify the entry and can be modified by Maestro. The title can be set or changed by the user, but is not otherwise modified by Maestro.

Once an entry has been incorporated into the project, its structures and their data are represented by a row in the Project Table. Each row contains the row number, an icon indicating whether the entry is displayed in the Workspace (the In column), the entry title, a button to open the Surfaces panel if the entry has surfaces, the entry name, and any entry properties. The row number is not a property of the entry.

Entries can be collected into groups, and the members of the group can be displayed or hidden. Most additions of multiple entries to the Project Table are done as entry groups.

You can use entries as input for all of the computational programs—Glide, Impact, Jaguar, Liaison, LigPrep, MacroModel, Phase, Prime, QikProp, QSite, and Strike. You can select entries as input for the ePlayer, which displays the selected structures in sequence. You can also duplicate, combine, rename, and sort entries; create properties; import structures as entries; and export structures and properties from entries in various formats.

To open the Project Table panel, do one of the following:

- Click the Open/Close Project Table button on the toolbar

- Choose Show Table from the Project menu
- Press CTRL+T.

The Project Table panel contains a menu bar, a toolbar, and the table itself.

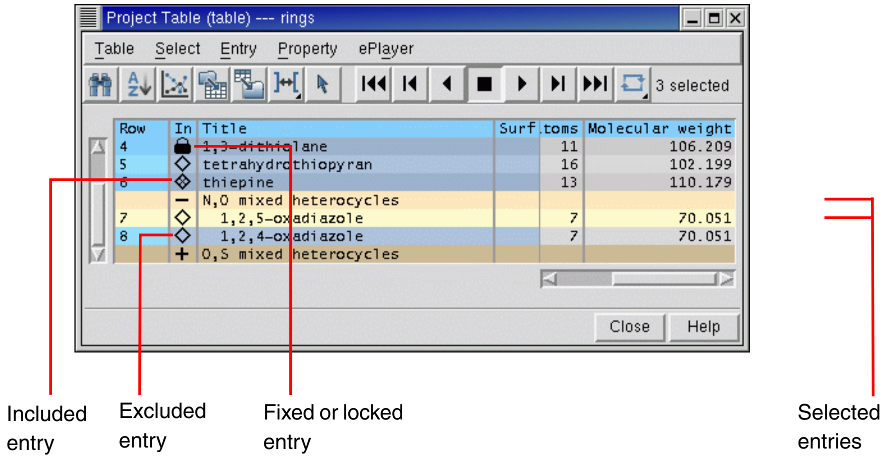


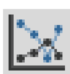
Figure 2.3. The Project Table ***panel.***

2.4.1 The Project Table Toolbar

The Project Table toolbar contains two groups of buttons and a status display. The first set of buttons opens various panels that allow you to perform functions on the entries in the Project Table. The second set of buttons controls the ePlayer, which "plays through" the selected structures: each structure is displayed in the Workspace in sequence, at a given time interval. See Section 2.3.2 on page 7 for a description of the types of toolbar buttons. The buttons are described below.

Find
Open the Find panel for locating alphanumeric text in any column of the Project Table, except for the row number.

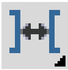
Sort
Open the Sort panel for sorting entries by up to three properties.



Plot
Open the Plot panel for plotting entry properties.

Import Structure
Open the Import panel for importing structures into the project.

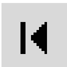
Export Structure
Open the Export panel for exporting structures to a file.



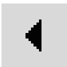
Columns
Choose an option for adjusting the column widths.

Select only
Open the Entry Selection dialog box for selecting entries based on criteria for entry properties.

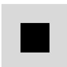
Go to start
Display the first selected structure.



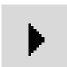
Previous
Display the previous structure in the list of selected structures.



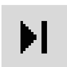
Play backward
Display the selected structures in sequence, moving toward the first.



Stop
Stop the ePlayer.

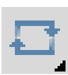


Play forward
Display the selected structures in sequence, moving toward the last.



Next
Display the next structure in the list of selected structures.

Go to end
Display the last selected structure.



Loop
Choose an option for repeating the display of the structures. Single Direction displays structures in a single direction, then repeats. Oscillate reverses direction each time the beginning or end of the list is reached.

The status display, to the right of the toolbar buttons, shows the number of selected entries. When you pause the cursor over the status display, the Balloon Help shows the total number of entries, the number shown in the table, the number selected, and the number included in the Workspace.

2.4.2 The Project Table Menus

- Table—find text, sort entries, plot properties, import and export structures, and configure the Project Table.
- Select—select all entries, none, invert your selection, or select classes of entries using the Entry Selection dialog box and the Filter panel.

- Entry—include or exclude entries from the Workspace, display or hide entries in the Project Table, and perform various operations on the selected entries.
- Property—display and manipulate entry properties in the Project Table.
- ePlayer—view entries in succession, stop, reverse, and set the ePlayer options.

2.4.3 Selecting Entries

Many operations in Maestro are performed on the entries selected in the Project Table. The Project Table functions much like any other table: select rows by clicking, shift-clicking, and control-clicking. However, because clicking in an editable cell of a selected row enters edit mode, you should click in the Row column to select entries. See Section 2.4.5 on page 16 for more information on mouse actions in the Project Table. There are shortcuts for selecting classes of entries on the Select menu.

In addition to selecting entries manually, you can select entries that meet a combination of conditions on their properties. Such combinations of conditions are called *filters*. Filters are Entry Selection Language (ESL) expressions and are evaluated at the time they are applied. For example, if you want to set up a Glide job that uses ligands with a low molecular weight (say, less than 300) and that has certain QikProp properties, you can set up a filter and use it to select entries for the job. If you save the filter, you can use it again on a different set of ligands that meet the same selection criteria.

To create a filter:

1. Do one of the following:
   - Choose Only, Add, or Deselect from the Select menu.
   - Click the Entry selection button on the toolbar.

2. In the Properties folder, select a property from the property list, then select a condition.
3. Combine this selection with the current filter by clicking Add, Subtract, or Intersect. These buttons perform the Boolean operations OR, AND NOT, and AND on the corresponding ESL expressions.
4. To save the filter for future use click Create Filter, enter a name, and click OK.
5. Click OK to apply the filter immediately.

2.4.4 Including Entries in the Workspace

In addition to selecting entries, you can also use the Project Table to control which entries are displayed in the Workspace. An entry that is displayed in the Workspace is *included* in the Workspace; likewise, an entry that is not displayed is *excluded*. Included entries are marked by an X in the diamond in the In column; excluded entries are marked by an empty diamond. Entry inclusion is completely independent of entry selection.

To include or exclude entries, click, shift-click, or control-click in the In column of the entries, or select entries and choose Include or Exclude from the Entry menu. Inclusion with the mouse works just like selection: when you include an entry by clicking, all other entries are excluded.

It is sometimes useful to keep one entry in the Workspace and include others one by one: for example, a receptor and a set of ligands. You can fix the receptor in the Workspace by selecting it in the Project Table and choosing Fix from the Entry menu or by pressing CTRL+F. A padlock icon replaces the diamond in the In column to denote a *fixed* entry. To remove a fixed entry from the Workspace, you must exclude it explicitly (CTRL+X). It is not affected by the inclusion or exclusion of other entries. Fixing an entry affects only its inclusion; you can still rotate, translate, or modify the structure.

2.4.5 Mouse Functions in the Project Table

The Project Table supports the standard use of shift-click and control-click to select objects. This behavior applies to the selection of entries and the inclusion of entries in the Workspace. You can also drag to resize rows and columns and to move rows.

You can drag a set of non-contiguous entries to reposition them in the Project Table. When you release the mouse button, the entries are placed after the first unselected entry that precedes the entry on which the cursor is resting. For example, if you select entries 2, 4, and 6, and release the mouse button on entry 3, these three entries are placed after entry 1, because entry 1 is the first unselected entry that precedes entry 3. To move entries to the top of the table, drag them above the top of the table; to move entries to the end of the table, drag them below the end of the table.

A summary of mouse functions in the Project Table is provided in Table 2.3.

Table 2.3. Mouse operations in the Project Table.

Task	Mouse Operation
Change a Boolean property value	Click repeatedly in a cell to cycle through the possible values (On, Off, Clear)
Display the Entry menu for an entry	Right-click anywhere in the entry. If the entry is not selected, it becomes the selected entry. If the entry is selected, the action is applied to all selected entries.
Display a version of the Property menu for a property	Right-click in the column header
Edit the text or the value in a table cell	Click in the cell and edit the text or value
Include an entry in the Workspace, exclude all others	Click the In column of the entry
Move selected entries	Drag the entries
Paste text into a table cell	Middle-click
Resize rows or columns	Drag the boundary with the middle mouse button
Select an entry, deselect all others	For an unselected entry, click anywhere in the row except the In column; for a selected entry, click the row number.
Select or include multiple entries	Click the first entry then shift-click the last entry
Toggle the selection or inclusion state	Control-click the entry or the In column

2.4.6 Project Table Shortcut Keys

Some frequently used project operations have been assigned shortcut key combinations. The shortcuts, their functions, and their menu equivalents are listed in Table 2.4.

Table 2.4. Shortcut keys in the Project Table.

Keys	Action	Equivalent Menu Choices
CTRL+A	Select all entries	Select > All
CTRL+F	Fix entry in Workspace	Entry > Fix
CTRL+I	Open Import panel	Table > Import Structures
CTRL+N	Include only selected entries	Entry > Include Only
CTRL+U	Deselect all entries	Select > None
CTRL+X	Exclude selected entries	Entry > Exclude
CTRL+Z	Undo/Redo last command	Edit > Undo/Redo in main window

2.5 Building a Structure

After you start Maestro, the first task is usually to create or import a structure. You can open existing Maestro projects or import structures from other sources to obtain a structure, or you can build your own. To open the Build panel, do one of the following:

- Click the Open/Close Build panel button in the toolbar:

- Choose Build from the Edit menu.
- Press CTRL+B.

The Build panel allows you to create structures by drawing or placing atoms or fragments in the Workspace and connecting them into a larger structure, to adjust atom positions and bond orders, and to change atom properties. This panel contains a toolbar and three folders.

2.5.1 Placing and Connecting Fragments

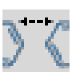
The Build panel provides several tools for creating structures in the Workspace. You can place and connect fragments, or you can draw a structure freehand.

To place a fragment in the Workspace:

1. Select Place.
2. Choose a fragment library from the Fragments menu.
3. Click a fragment.
4. Click in the Workspace where you want the fragment to be placed.

To connect fragments in the Workspace, do one of the following:

- Place another fragment and connect them using the Connect & Fuse panel, which you open from the Edit menu on the main menu bar or with the Display Connect & Fuse panel on the Build toolbar.



- Replace one or more atoms in the existing fragment with another fragment by selecting a fragment and clicking in the Workspace on the main atom to be replaced.
- Grow another fragment by selecting Grow in the Build panel and clicking the fragment you want to add in the Fragments folder.

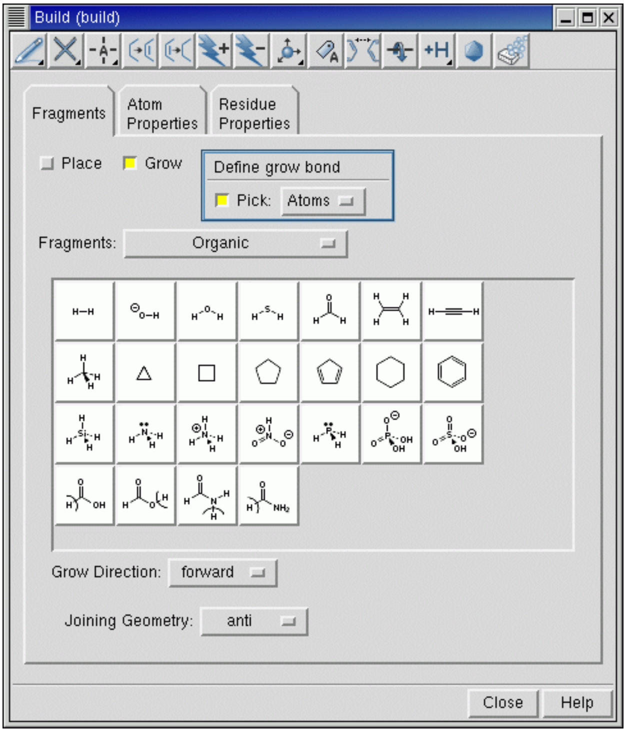
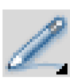


Figure 2.4. The* Build *panel.

Grow mode uses predefined rules to connect a fragment to the *grow bond*. The grow bond is marked by a green arrow. The new fragment replaces the atom at the head of the arrow on the grow bond and all atoms attached to it. To change the grow bond, choose Bonds from the Pick option menu in the Build panel and click on the desired grow bond in the Workspace. The arrow points to the atom nearest to where you clicked.

To draw a structure freehand:

1. Choose an element from the Draw button menu on the Build panel toolbar:



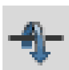
2. Click in the Workspace to place an atom of that element.
3. Click again to place another atom and connect it to the previous atom.
4. Continue this process until you have drawn the structure.
5. Click the active atom again to finish drawing.

2.5.2 Adjusting Properties

In the Atom Properties folder, you can change the properties of the atoms in the Workspace. For each item on the Property option menu—Element, Atom Type (MacroModel), Partial Charge, PDB Atom Name, Grow Name, and Atom Name—there is a set of tools you can use to change the atom properties. For example, the Element tools consist of a periodic table from which you can choose an element and select an atom to change it to an atom of the selected element.

Similarly, the Residue Properties folder provides tools for changing the properties of residues: the Residue Number, the Residue Name, and the Chain Name.

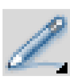
To adjust bond lengths, bond angles, dihedral angles, and chiralities during or after building a structure, use the Adjust distances, angles or dihedrals button on the main toolbar:



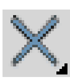
You can also open the Adjust panel from this button menu, from the Display Adjust panel button on the Build panel toolbar (which has the same appearance as the above button) or from the Edit menu in the main window.

2.5.3 The Build Panel Toolbar

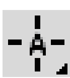
The toolbar of the Build panel provides quick access to tools for drawing and modifying structures and labeling atoms. See Section 2.3.2 on page 7 for a description of the types of toolbar buttons. The toolbar buttons and their use are described below.



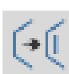
Free-hand drawing
Choose an element for drawing structures freehand in the Workspace (default C). Each click in the Workspace places an atom and connects it to the previous atom.



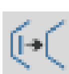
Delete
Choose an object for deleting. Same as the Delete button on the main toolbar, see page 8.



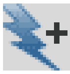
Set element
Choose an element for changing atoms in the Workspace (default C). Click an atom to change it to the selected element.



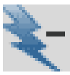
Increment bond order
Select a bond to increase its bond order by one, to a maximum of 3.



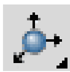
Decrement bond order
Select a bond to decrease its bond order by one, to a minimum of 0.



Increment formal charge
Select an atom to increase its formal charge by one.

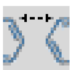


Decrement formal charge
Select an atom to decrease its formal charge by one.



Move
Choose a direction for moving atoms, then click the atom to be moved. Moves in the XY plane are made by clicking the new location. Moves in the Z direction are made in 0.5 Å increments.

Label
Apply heteroatom labels as you build a structure. The label consists of the element name and formal charge, and is applied to atoms other than C and H.



Display Connect & Fuse panel
Open the Connect & Fuse panel so you can connect structures (create bonds between structures) or fuse structures (replace atoms of one structure with those of another).

Display Adjust panel
Open the Adjust panel so you can change bond lengths, bond angles, dihedral angles, or atom chiralities.

Add hydrogens
Choose an atom type for applying the current hydrogen treatment. Same as the Add hydrogens button on the main toolbar, see page 8.

Geometry Symmetrizer
Open the Geometry Symmetrizer panel for symmetrizing the geometry of the structure in the Workspace.

Geometry Cleanup
Clean up the geometry of the structure in the Workspace.

2.6 Selecting Atoms

Maestro has a powerful set of tools for selecting atoms in a structure: toolbar buttons, picking tools in panels, and the Atom Selection dialog box. These tools allow you to select atoms in two ways:

- Select atoms first and apply an action to them
- Choose an action first and then select atoms for that action

2.6.1 Toolbar Buttons

The small triangle in the lower right corner of a toolbar button indicates that the button contains a menu. Many of these buttons allow you to choose an object type for selecting: choose Atoms, Bonds, Residues, Chains, Molecules, or Entries, then click on an atom in the Workspace to perform the action on all the atoms in that structural unit.

For example, to select atoms with the Workspace selection toolbar button:

1. Choose Residues from the Workspace selection button menu:

   The button changes to:

2. Click on an atom in a residue in the Workspace to select all the atoms in that residue.

2.6.2 Picking Tools

The picking tools are embedded in each panel in which you need to select atoms to apply an operation. The picking tools in a panel can include one or more of the following:

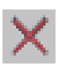
- Pick option menu—Allows you to choose an object type. Depending on the operation to be performed, you can choose Atoms, Bonds, Residues, Chains, Molecules, or Entries, then click on an atom in the Workspace to perform the action on all the atoms in that structural unit.

  The Pick option menu varies from panel to panel, because not all object types are appropriate for a given operation. For example, some panels have only Atoms and Bonds in the Pick option menu.

- All button—Performs the action on all atoms in the Workspace.
- Selection button—Performs the action on any atoms already selected in the Workspace.
- Previous button—Performs the action on the most recent atom selection defined in the Atom Selection dialog box.
- Select button—Opens the Atom Selection dialog box.
- ASL text box—Allows you to type in an ASL expression for selecting atoms.

  ASL stands for Atom Specification Language, and is described in detail in the *Maestro Command Reference Manual*.

- Clear button—Clears the current selection

- Show markers option—Marks the selected atoms in the Workspace.

For example, to label atoms with the Label Atoms panel:

1. Choose Atom Labels from the Display menu.
2. In the Composition folder, select Element and Atom Number.
3. In the picking tools section at the top of the panel, you could do one of the following:
   - Click Selection to apply labels to the atoms already selected in the Workspace (from the previous example).
   - Choose Residues from the Pick option menu and click on an atom in a different residue to label all the atoms in that residue.

2.6.3 The Atom Selection Dialog Box

If you wish to select atoms based on more complex criteria, you can use the Atom Selection dialog box. To open this dialog box, choose Select from a button menu or click the Select button in a panel. See Section 5.3 of the *Maestro User Manual* for detailed instructions on how to use the Atom Selection dialog box.

2.7 Scripting in Maestro

Although you can perform nearly all Maestro-supported operations through menus and panels, you can also perform operations using Maestro commands, or compilations of these commands, called *scripts*. Scripts can be used to automate lengthy procedures or repetitive tasks and can be created in several ways. These are summarized below.

2.7.1 Python Scripts

Python is a full-featured scripting language that has been embedded in Maestro to extend its scripting facilities. The Python capabilities within Maestro include access to Maestro functionality for dealing with chemical structures, projects, and Maestro files.

The two main Python commands used in Maestro are:

- `pythonrun`—executes a Python module. (You can also use the alias `pyrun`.) The syntax is:

  `pythonrun` *module*.*function*

- `pythonimport`—rereads a Python file so that the next time you use the `pythonrun` command, it uses the updated version of the module. (You can also use the alias `pyimp`.)

From the Maestro Scripts menu you can install, manage, and run Python scripts. For more information on the Scripts menu, see Section 13.1 of the *Maestro User Manual*.

For more information on using Python with Maestro, see *Maestro Scripting with Python*.

2.7.2 Command Scripts

All Maestro commands are logged and displayed in the Command Script Editor panel. This means you can create a command script by performing the operations with the GUI controls, copying the logged commands from the Command History list into the Script text area of the panel, then saving the list of copied commands as a script.

To run an existing command script:

1. Open the Command Script Editor panel from the Edit menu in the main window.
2. Click Open Local and navigate to the directory containing the desired script.
3. Select a script in the Files list and click Open.

   The script is loaded into the Script window of the Command Script Editor panel.
4. Click Run Script.

Command scripts cannot be used for Prime operations.

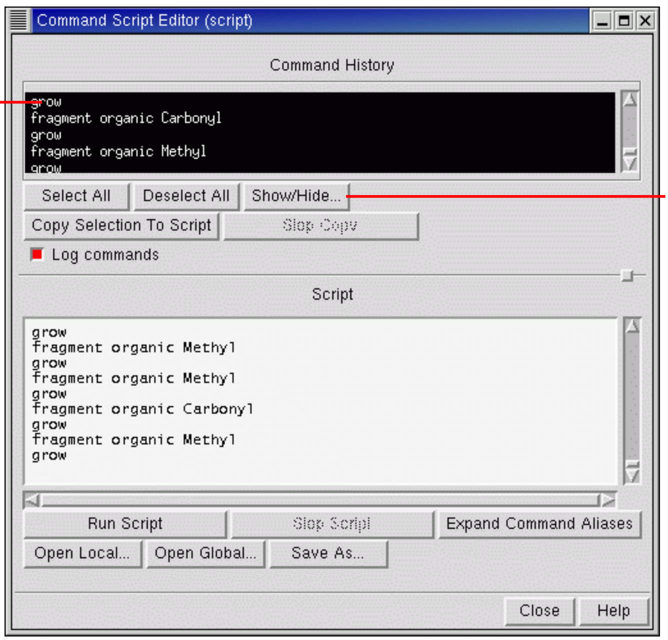


Figure 2.5. The Command Script Editor ***panel.***

2.7.3 Macros

There are two kinds of macros you can create: named macros and macros assigned to function keys F1 through F12.

To create and run a named macro:

1. Open the Macros panel from the Edit menu in the main window.
2. Click New, enter a name for the macro, and click OK.
3. In the Definition text box, type the commands for the macro.
4. Click Update to update the macro definition.
5. To run the macro, enter the following in the command input area in the main window:

   `macrorun` *macro-name*

   If the command input area is not visible, choose Command Input Area from the Display menu.

To create and run a function key macro:

1. Open the Function Key Macros panel from the Edit menu in the main window.
2. From the Macro Key option, select a function key (F1 through F12) to which to assign the macro.
3. In the text box, type the commands for the macro.
4. Click Run to test the macro or click Save to save it.
5. To run the macro from the main window, press the assigned function key.

For more information on macros, see Section 13.5 of the *Maestro User Manual*.

2.8 Specifying a Maestro Working Directory

When you use Maestro to launch MacroModel jobs, Maestro writes job output to the directory specified in the Directory folder of the Preferences panel. By default, this directory (the file I/O directory) is the directory from which you started Maestro.

To change the Maestro working directory:

1. Open the Preferences panel from the Maestro menu.
2. Click the Directory tab.
3. Select the directory you want to use for reading and writing files.

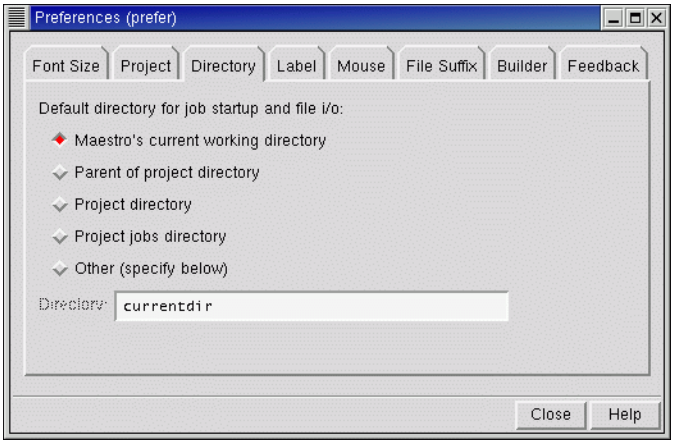


Figure 2.6. T

You can also set other preferences in the Preferences panel. See Section 12.2 of the *Maestro User Manual* for details.

2.9 Undoing an Operation

To undo a single operation, click the Undo button in the toolbar, choose Undo from the Edit menu, or press CTRL+Z. The word Undo in the menu is followed by text that describes the operation to undo. Not all operations can be undone: for example, global rotations and translations are not undoable operations. For such operations you can use the Save view and Restore view buttons in the toolbar, which save and restore a molecular orientation.

2.10 Running and Monitoring Jobs

Maestro has panels for each product for preparing and submitting jobs. To use these panels, choose the appropriate product and task from the Applications menu and its submenus. Set the appropriate options in the panel, then click Start to open the Start dialog box and set options for running the job. For a complete description of the Start dialog box associated with your computational program, see your product's User Manual. When you have finished setting the options, click Start to launch the job and open the Monitor panel.

The Monitor panel is the control panel for monitoring the progress of jobs and for pausing, resuming, or killing jobs. All jobs that belong to your user ID can be displayed in the Monitor panel, whether or not they were started from Maestro. Subjobs are indented under their parent in the job list. The text pane shows various output information from the monitored job, such as the contents of the log file. The Monitor panel opens automatically when you start a job. If it is

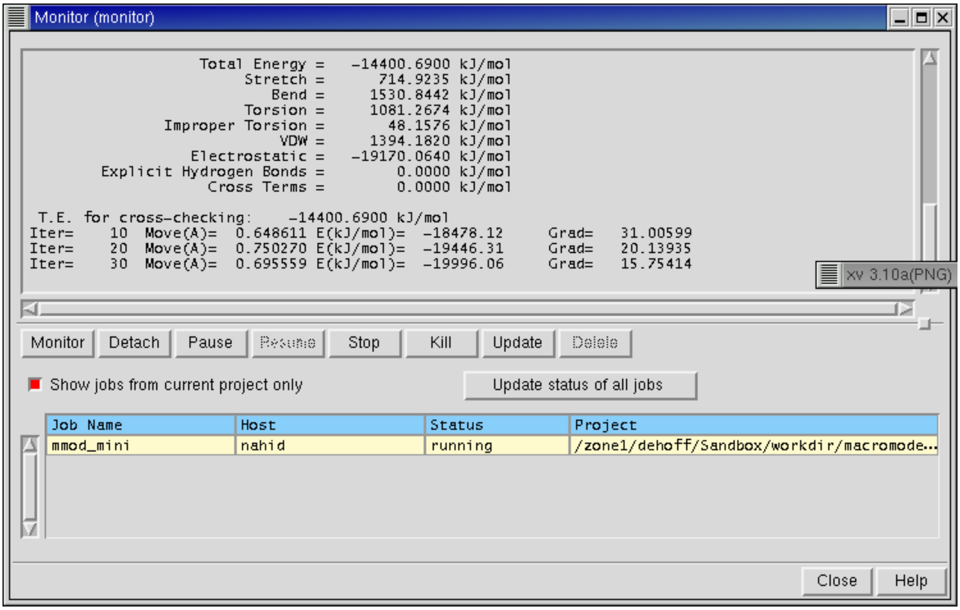


Figure 2.7. The Monitor ***panel.***

not open, you can open it by choosing Monitor from the Applications menu in the Maestro main window.

While jobs are running, the Detach, Pause, Resume, Stop, Kill, and Update buttons are active. When there are no jobs currently running, only the Monitor and Delete buttons are active. These buttons act on the selected job. By default, only jobs started from the current project are shown. To show other jobs, deselect Show jobs from current project only.

When a monitored job ends, the results are incorporated into the project according to the settings used to launch the job. If a job that is not currently being monitored ends, you can select it in the Monitor panel and click Monitor to incorporate the results. Monitored jobs are incorporated only if they are part of the current project. You can monitor jobs that are not part of the current project, but their results are not incorporated. To add their results to a project, you must open the project and import the results.

Further information on job control, including configuring your site, monitoring jobs, running jobs, and job incorporation, can be found in the *Job Control Guide* and the *Installation Guide*.

2.11 Getting Help

Maestro comes with automatic, context-sensitive help (Auto-Help), Balloon Help (tooltips), an online help facility, and a user manual. To get help, follow the steps below:

- Check the Auto-Help text box at the bottom of the main window. If help is available for the task you are performing, it is automatically displayed there. It describes what actions are needed to perform the task.
- If your question concerns a GUI element, such as a button or option, there may be Balloon Help for the item. Pause the cursor over the element. If the Balloon Help does not appear, check that Show Balloon Help is selected in the Help menu of the main window. If there is Balloon Help for the element, it appears within a few seconds.
- If you do not find the help you need using either of the steps above, click the Help button in the lower right corner of the appropriate panel. The Help panel is displayed with a relevant help topic.
- For help with a concept or action not associated with a panel, open the Help panel from the Help menu or press CTRL+H.

If you do not find the information you need in the Maestro help system, check the following sources:

- The *Maestro User Manual*
- The Frequently Asked Questions page, found at http://www.schrodinger.com/Support/faq.html

You can also contact Schrödinger by e-mail or phone for help:

- E-mail: help@schrodinger.com
- Phone: (503) 299-1150

2.12 Ending a Maestro Session

To end a Maestro session, choose Quit from the Maestro menu. To save a log file with a record of all operations performed in the current session, click Quit, save log file in the Quit panel. This information can be useful to Schrödinger support staff when responding to any problem you report.

QuickTopics

3.1 Introduction

This chapter is designed to help you become familiar with the functionality of MacroModel 9.1. Once you have worked through these exercises, you will have an understanding of the basic MacroModel features. Please note that these exercises are didactic in nature and that the computations presented are not meant to be converged. For a tutorial introduction to the basic features of Maestro, see the *Maestro Tutorial*.

Maestro comes with automatic context-sensitive help (Auto-Help), Balloon Help (tooltips), an online help facility, and a user manual. For more information, see Section 2.11 on page 28. You can also undo some operations in Maestro. For more information, see Section 2.9 on page 26.

3.2 Preparing for the Exercises

To complete the exercises, you must have access to an installed version of Maestro 7.5 and MacroModel 9.1. For installation instructions, see the *Installation Guide*. Before you start these exercises, it is a good idea to create a working directory, see below.

The `$SCHRODINGER/macromodel-v`*version*`/samples/QuickTopics` directory of your MacroModel distribution contains the structure files used in the following exercises. This directory is referred to from here on as the `QuickTopics` directory. The `QuickTopics` directory also contains sample input files. If you want, you can copy these files to your working directory to run later QuickTopics exercises without having to complete all of the preceding exercises. You will create your own output when you perform the exercises in this guide.

To create the working directory:

1. Change to a directory in which you have write permission.
2. Create a directory by entering the command:

   `mkdir` *working-directory-name*

Once you have created a working directory, you can start Maestro. If you change to the working directory before starting Maestro, this directory automatically becomes your working directory in Maestro.

To start Maestro:

1. Set the SCHRODINGER environment variable to the directory in which Maestro and MacroModel are installed:

   csh/tcsh: `setenv SCHRODINGER` *installation_path*

   sh/bash/ksh: `export SCHRODINGER=`*installation_path*

2. Change to the desired working directory.

   `cd` *working-directory-name*

3. Enter the command:

   `$SCHRODINGER/maestro &`

When you use Maestro to launch MacroModel jobs, Maestro writes job output to the directory specified in the Directory folder of the Preferences panel. By default, the directory to which Maestro writes files (the file I/O directory) is the directory you were in when you started Maestro. If you want the output files placed in another directory, you can change the preferences as described in Section 2.8 on page 25.

3.3 Introduction to Maestro: Modeling with a Protein-Ligand Complex

The exercises in this section present a quick tour of the Maestro interface, including the following:

- Importing and exporting a structure file
- Deleting portions of a Workspace structure
- Using the Find feature to locate particular structural elements
- Displaying, undisplaying, and labeling atoms and molecules
- Choosing selection states and selecting objects in the Workspace
- Manipulating the structure in other ways

You can find additional information about Maestro in the *Maestro User Manual*, and an introduction to building, adjusting, displaying, and representing structures in the *Maestro Tutorial*.

The following exercises use the structure in `1err.pdb`. This structure is located in the `QuickTopics` directory.

3.3.1 Importing the Complex into the Project

To display an existing structure in the Workspace, you must import the structure into the current project. Follow the instructions below to import the `1err` protein-ligand complex.

1. Click the Open/Close Project Table toolbar button, or choose Show Table from the Project menu in the main window.

2. Choose New from the Project menu in the main window.
3. In the Project text box, enter `1err.prj` at the end of the path name and click Create.
4. Click the Import structures button on the main toolbar.

The Import panel opens (see Figure 3.1).

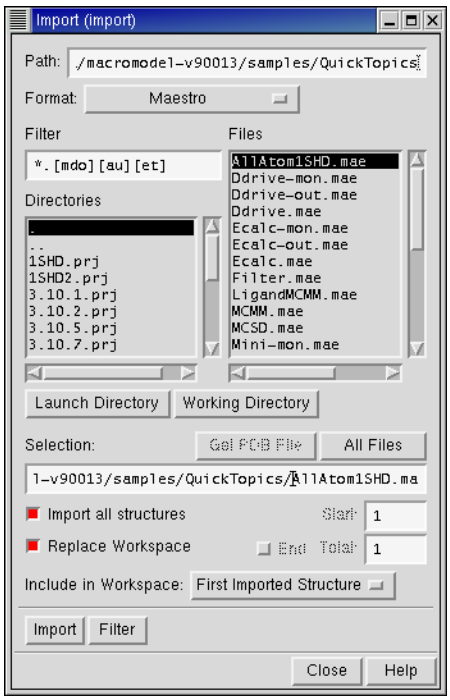


Figure 3.1. The* Import *panel.

You can also open the Import panel by choosing Import Structures from the Project menu in the main window or by choosing Structures from the Import submenu of the Table menu in the Project Table panel.

5. Choose PDB from the Format option menu.
6. Navigate to the `QuickTopics` directory and select `1err.pdb`. The path is:

   `$SCHRODINGER/macromodel-v`*version*`/samples/QuickTopics`

7. Click Import.

   A warning dialog box appears, but it isn't critical for this exercise. Click OK.

8. In the Import panel, click Close.

When Maestro imports a PDB file, problematic parts of imported structures, such as non-standard functional groups, are colored orange, red, green, or blue. For this exercise, it is not necessary to correct the protein structure. However, when you begin to work on other proteins, you may want to investigate and manually adjust marked portions. See Section 3.1.3 of the *Maestro User Manual* for more information.

3.3.2 Identifying, Labeling, and Deleting Structure Elements

This exercise demonstrates how to use Maestro's display tools to inspect the protein-ligand complex and delete parts of the structure that are not needed for a calculation.

The protein-ligand complex imported in the last exercise was obtained from the Protein Data Bank repository. The structure contains crystallographic water molecules, which need to be removed. Also, the structure is dimeric, and for most purposes only the monomer is required.

To label the water molecules with the PDB name:

1. In the Workspace, right-click on an atom in one of the outlying water molecules to spot-center on the atom.
2. Zoom in on the area containing the water molecules by holding down the middle and right mouse buttons and dragging the mouse to the right, until you have a good view of the water molecules.
3. Choose Composition from the Label picked atoms button menu.

   The Atom Labels panel opens (see Figure 3.2)

4. Choose Molecules from the Label atoms pick menu.

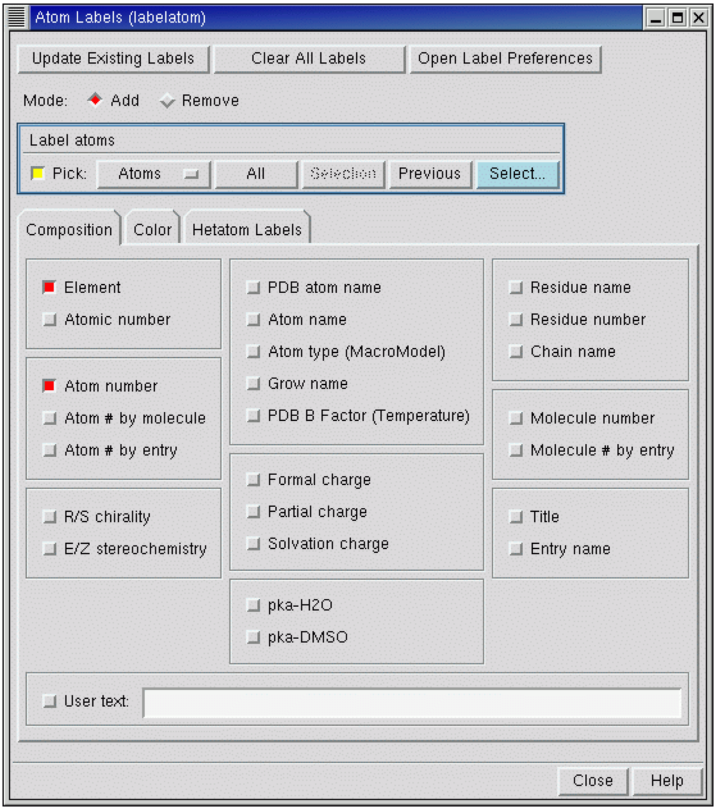
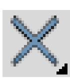


Figure 3.2. The Atom Labels ***panel showing the*** Composition ***folder.***

5. In the Composition folder, select Residue name and clear all other selections.
6. In the Workspace, select one of the outlying water molecules of the structure to display its label: HOH.
7. Close the Atom Labels panel.

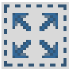
To delete unwanted atoms:

1. Choose Waters from the Delete button menu.



All the water molecules are deleted.

2. Click the Fit to screen button.

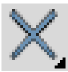


The entire protein is now visible.

3. Pause the pointer over various atoms in the protein until you find one that is in chain B.

   Information on an atom is displayed in the status area when the pointer pauses over the atom, beginning with the chain name.

4. Choose Chains from the Delete button menu, and click on an atom in chain B.



The entire chain, including the ligand, is deleted, leaving chain A.

3.3.3 Using the Find Atoms Panel to Identify Molecules

The imported structure contains three discrete molecules. Find and visualize the three separate molecules with the Find Atoms panel:

1. From the Edit menu, choose Find to open the Find Atoms panel (see Figure 3.3).
2. Under Find types, choose Molecule.
3. Enter `1` in the Molecule number text box.
4. Select Mark found atoms and Center.

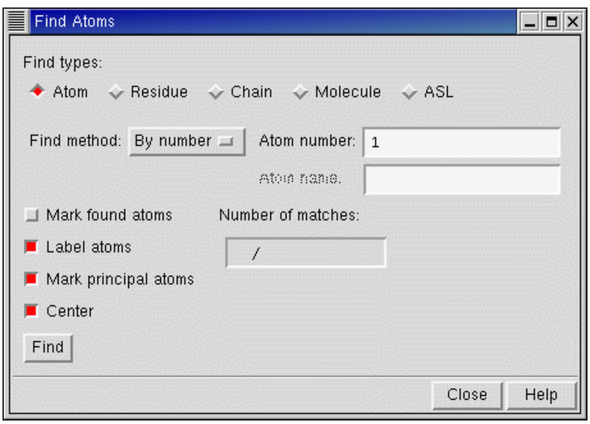


Figure 3.3. The* Find Atoms *panel.

5. Click Find.
6. Repeat this process to identify molecules 2, 3, and 4. Molecule 4 is the ligand.
7. When you have finished finding the molecules, clear all the options in the lower left of the panel and close the Find panel.

3.3.4 Identifying Molecules Using Coloring Schemes

Another method to view multi-molecule structures is by coloring a structure "by molecule." This exercise demonstrates how to apply the Molecule Number coloring scheme to the structure in the Workspace.

1. Choose Molecule Number from the Color all atoms by scheme button menu to color each molecule a different color.

2. Now choose Molecule Number (Carbons) from the button menu.

   This coloring scheme allows you to both distinguish molecules from one another and to determine the elemental identity of heteroatoms.

You can also color atoms using the Atom Coloring panel: choose Atom Coloring from the Display menu in the main window.

3.3.5 Exploring Molecular Representation Styles

You may find it useful to distinguish the ligand from the protein by using a different molecular representation. You can explore the different representation styles in the *Maestro Tutorial*. For proteins, you can visualize the secondary structure by displaying the residues as ribbons. Non-peptide parts of the structure are retained in their existing atomic representation.

1. Choose Show Ribbons from the Show, hide, or color ribbons button menu.

2. The receptor is displayed in the default ribbon style and color scheme, and the receptor atoms are hidden. The ligand representation does not change.
3. Choose Secondary structure from the Show, hide, or color ribbons button menu.

   The ribbon is colored according to the type of secondary structure.

4. Choose Show ribbons and atoms from the Show, hide, or color ribbons button menu.

   The receptor atoms are redisplayed.

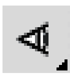
5. Choose Hide ribbons from the Show, hide, or color ribbons button menu.

   The ribbons are undisplayed.

3.3.6 Displaying and Undisplaying Atoms

By undisplaying atoms that do not contribute to active site functionality, you can more easily examine the active site. Atoms can be displayed and undisplayed in the Workspace using the toolbar, the Display/Undisplay Atoms panel, or by entering an `undisplayatom` command with an appropriate Atom Specification Language (ASL) expression in the command input area. Below are instructions for using the toolbar. For information on the other methods, see Section 6.4 of the *Maestro User Manual*.

1. Choose Select from the Display only button menu.

2. The Atom Selection dialog box opens (see Figure 3.4).

3. In the Molecule folder, choose Molecule Number from the list on the left and enter `4` in the Molecule Number text box.

4. Click Add, then click OK.

   The ligand, which is molecule number 4, is displayed and the remaining atoms are undisplayed.

5. Choose Protein Backbone from the Also display button menu. Repeat for Protein Side Chains and for Waters.

You have now redisplayed the entire protein. However, the crystallographic water molecules have not been redisplayed because they were deleted, not undisplayed, in the exercise in Section 3.3.2 on page 32.

You can also display residues that have atoms within a specified distance of the currently displayed atoms. This is useful for displaying the part of a protein that is close to a ligand.

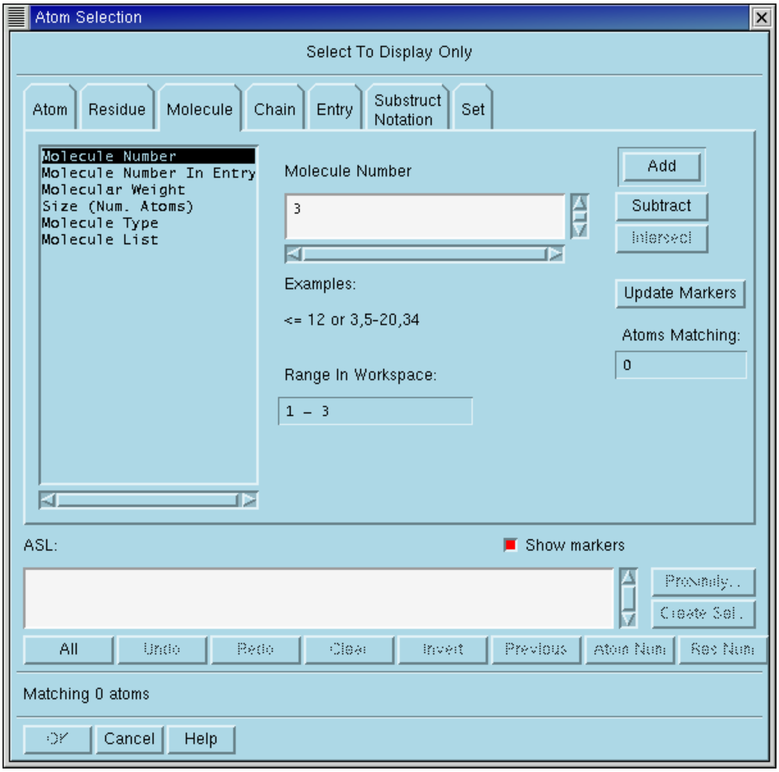
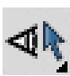


Figure 3.4. The Atom Selection ***dialog box,*** Molecule ***folder.***

1. Choose Molecules from the Display only selected atoms button menu.



2. Click on an atom in the ligand to display only the ligand.
3. Choose +8 Angstroms from the Display atoms within N Angstroms of currently displayed atoms button menu.

For more complicated atom selections, you can use the Display/Undisplay Atoms panel (choose Display/Undisplay Atoms from the Display menu).

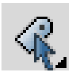
4. Redisplay all atoms by choosing All from the Also display button menu.

3.3.7 Applying and Removing Atom Labels

You can apply labels to any atoms in the Workspace. You can also specify the label content, label placement, and label appearance. In the exercise in Section 3.3.2 on page 32, you labeled atoms with their PDB residue names. This exercise demonstrates how to apply and remove various types of atom labels.

To apply atom labels:

1. Choose Composition from the Label picked atoms button menu to open the Atom Labels panel.

2. In the Composition folder, select Atom number, Atom type (MacroModel), and Formal charge, and clear any other selections.
3. Under Label atoms, choose Molecules from the Pick menu.
4. In the Workspace, click on an atom in the ligand to label its atoms.

To remove atom labels:

1. Under Mode, select Remove (located at the top of the Atom Labels panel).

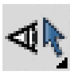
   The Label atoms section is renamed Clear labels, to reflect the mode change.
2. Click Select in the Clear labels section.

   The Atom Selection dialog box opens.
3. In the Atom folder, select Element from the list on the left, then select O from the Element list in the center.
4. Click Add, then click OK to remove the labels for all oxygen atoms.
5. In the Atom Labels panel, click All in the Clear Labels section to remove all atom labels.
6. Close the Atom Labels panel.

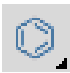
3.3.8 Adjusting Bond Orders, Atom Types, and Formal Charges

Most PDB structures derived from X-ray crystallography data do not have hydrogen atoms, formal charges, or bond orders. When the structure is imported into Maestro, the conversion utility uses templates for assigning multiple bonds in standard residues, but cannot do so for ligands. Thus you need to explicitly add multiple bonds and formal charges to the ligands if necessary. The tools for these tasks are found in the Build panel. The 1err ligand Raloxifene needs multiple bonds assigned, and the piperidine nitrogen adjusted to be a four-coordinate, positively charged ammonium group. In this exercise you will convert single bonds to double bonds and adjust formal charges where necessary. In the next exercise, the hydrogen atoms will be added.

1. Choose Molecules from the Display only selected atoms button menu and select an atom in the ligand. (You can choose Molecule Number from the Color all atoms by scheme button menu, to help distinguish the ligand.)

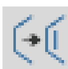
2. If the molecule is not displayed in wire representation, choose Molecule from the Draw bonds in wire button menu and select an atom in the ligand.

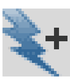
3. Choose Element from the Color all atoms by scheme button menu.

4. Open the Build panel (Open/Close Build panel toolbar button, Edit menu, or CTRL+B).
5. Click the Increment bond order button on the Build panel toolbar.

6. Click on the aryl C–C bonds that need to be converted to double bonds.
7. Click on the carbonyl C–O bond.
8. Click the Increment formal charge button on the Build panel toolbar.

9. Click on the nitrogen atom of the piperidine in the Workspace.

   The formal charge of the nitrogen atom is now +1, and the atom type is automatically adjusted. To check the formal charge, choose Formal Charge from the Label atoms button menu. Choose Delete Labels from the Label atoms button menu to remove the label.

Maestro also provides a tool for automatic assignment of bond orders. To use it, choose Assign Bond Orders from the Tools menu. Automatic assignments should always be checked, because the rules that are used for the assignments cannot cover every possibility.

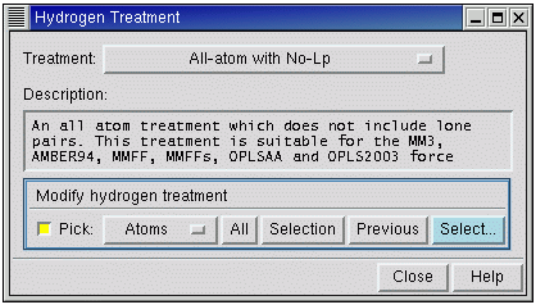


Figure 3.5. The Hydrogen Treatment ***panel.***

3.3.9 Adding Hydrogens to a United Atom Structure

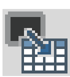
Modern force fields use all-atom structures, and Maestro contains a facility to rationally add the appropriate number of hydrogens to carbon atoms with approximately the correct geometry. This exercise demonstrates how to use the tools in the Hydrogen Treatment panel to add hydrogens to the structure in the Workspace.

1. From the Edit menu, choose Hydrogen Treatment.
2. Choose All-atom with No-Lp from the Treatments option menu (see Figure 3.5).
3. Under Modify hydrogen treatment, click All to add a full complement of hydrogens to the original structure.
4. Close the Hydrogen Treatment panel.

You can also add hydrogen atoms with the Add hydrogens toolbar button. This button applies the current hydrogen treatment to the selected atoms.

Now save the modified structure as a new entry in the project:

1. Click the Create entry from Workspace button in the toolbar.



2. Enter `1err_htreat` in the Entry name text box and click Create to update the Project Table with the new entry.

3.3.10 Displaying Hydrogen Bonds

This exercise demonstrates how to visualize hydrogen bonds and close contacts for the displayed structure.

1. Redisplay all atoms by choosing All from the Also display button menu.
2. Choose Molecule Number (Carbons) from the Color all atoms by scheme button menu.

   The carbon atoms are colored by the molecule number, and all other atoms are colored by element. This helps to distinguish the ligand, while still allowing you to identify the elements.
3. Choose Inter H-Bonds from the Display H-bonds button menu (located in the lower left corner of the main toolbar).

4. Pick an atom in the ligand.

   Yellow dashed lines connecting relevant atoms in the ligand and the receptor are displayed, indicating hydrogen bonds. Rotate the structure (drag with the middle mouse button) until these lines are visible. In this structure, there is a hydrogen bond from the piperidinium ion to a carbonyl oxygen in the receptor.

   If the hydrogen bonds are not displayed, choose Measurements from the Tools menu in the main window, click on the H-Bonds tab and select Display H-bonds.

You can also use the H-bonds folder in the Measurements panel to view hydrogen bonds between entities other than a single molecule. You can modify the H-bond display criteria by changing the values in the text boxes in the upper portion of the H-Bond folder.

You can also define and display close contacts by performing similar operations using the settings in the Contacts folder of the Measurements panel.

3.3.11 Exporting a Structure

Structures can be exported from Maestro to files in various formats. This exercise demonstrates how to export the structure currently displayed in the Workspace.

1. Open the Project Table panel (Open/Close Project Table toolbar button, choose Show Table from the Project menu, or press CTRL+T).

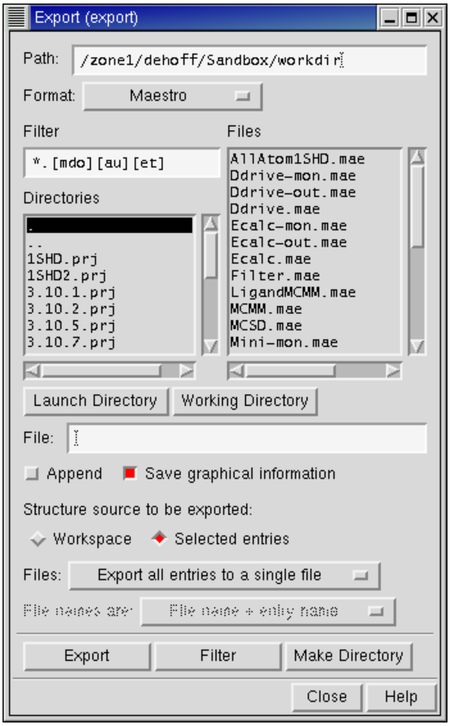


Figure 3.6. The Export ***panel.***

2. Select the `1err_htreat` entry.
3. Choose Structures from the Export submenu of the Table menu.

   The Export panel opens.
4. Choose Maestro from the Format option menu (see Figure 3.6).
5. Enter `1err_htreat.mae` in the File text box.
6. Under Structure source to be exported, select Selected entries.
7. Click Export, then click Close.

3.4 Creating and Viewing Surfaces

Examining the surface of a molecule frequently leads to valuable insights. Maestro can create several surface types. Surfaces can be rendered in different styles, color schemes, and transparency. Maestro surfaces are associated with project entries.

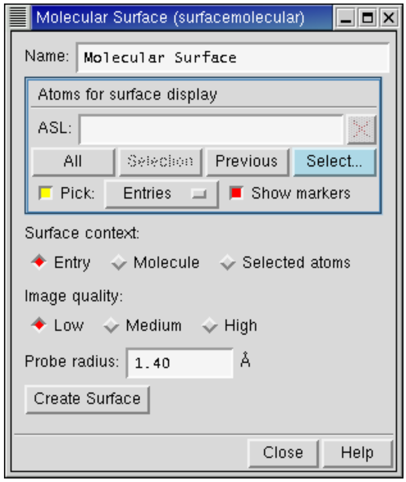


Figure 3.7. The* Molecular Surface *panel.

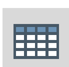
This set of exercises uses the `1err.prj` project from the previous section. If you are starting the tutorial at this point, follow the instructions in Section 3.3.1, Section 3.3.2, Section 3.3.8, and Section 3.3.9 to set up the project for these exercises.

3.4.1 Creating a Molecular Surface of a Complex

Maestro can create molecular surfaces that represent solvent-accessible regions of an entry. The molecular surface is a Connolly surface where a probe, typically with a radius of 1.4 Å, is rolled over the molecule. The surface is defined by the contact of the probe's outer radius and the molecule's van der Waals radius.

To generate a molecular surface for all atoms in the entry:

1. Open the Project Table panel (Open/Close Project Table toolbar button, choose Show Table from the Project menu, or press CTRL+T).



2. Click the In field for the `1err` entry to include it in the Workspace.
3. Choose Molecular Surface from the Surfaces submenu of the Display menu in the main window.

   The Molecular Surface panel opens (see Figure 3.7 on page 43).
4. Enter `MolSurf1` in the Name text box.

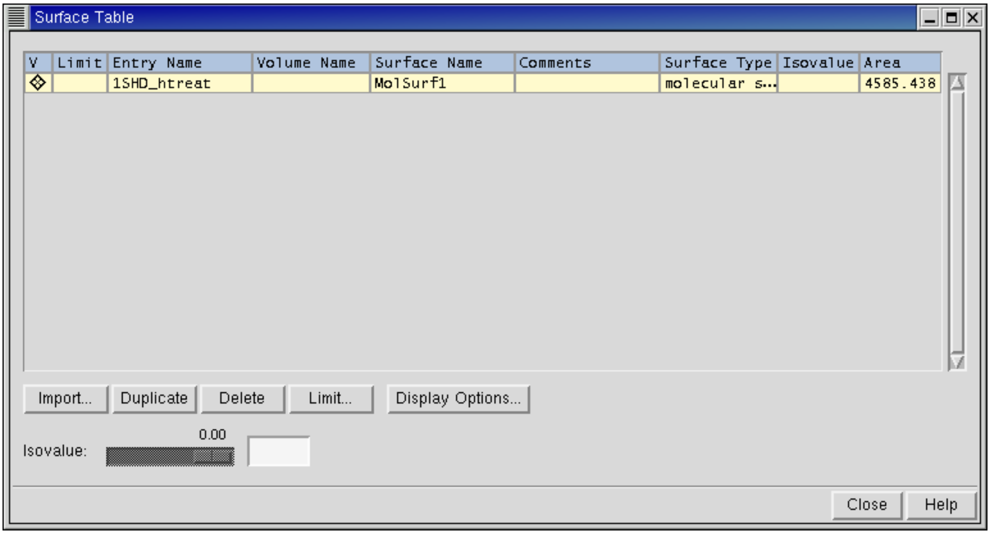


Figure 3.8. The Surface Table Panel ***panel.***

5. Under Atoms for surface display, choose Entries from the Pick menu.
6. Select Entries under Surface Context.

   The *surface context* describes the atoms for which the surface is created. The *surface display* describes the atoms for which the resulting surface is displayed. You can change the atoms for which the surface is displayed after surface generation by using the Limit feature, which you will do in the next exercise.
7. In the Workspace, select an atom in the entry.
8. Click Create Surface.

   When the surface generation is complete, the surface is displayed in the Workspace and the Surface Table panel is displayed (see Figure 3.8 on page 44).

You can experiment with the surfaces by doing any of the following:

- Generate the same surface with High image quality (give it a different name).

  This calculation takes longer to generate, but the resulting surface has superior quality. Also, the resulting high quality surface may be slower to rotate depending on your workstation resources.
- In the Surface Table panel, click Display Options and experiment with different styles and color schemes.

The Partial Charge color scheme uses white until a calculation is performed. The structure was imported from a PDB record, which has no information about the fractional atomic charges. Therefore, these must be calculated (see Section 3.6 on page 53) before Maestro can render the partial charge values on the surface.

3.4.2 Limits to a Surface

Frequently the entire surface of an entry is not required. Instead of creating another surface with a smaller subset of atoms, you can display a portion of a generated surface using the Limit panel. This exercise demonstrates how to limit the surface generated in the previous exercise from the entire entry to a smaller section of the entry.

1. In the Surface Table, click the V field of the `MolSurf1` entry to display it.
2. Click Limit (in the lower portion of the Surface Table panel) to open the Limit panel.
3. Enter `mol.num 1` in the ASL text box.
4. Click Apply to see the changes or OK to accept the changes.

   The surface is limited to the part that is generated for molecule number 1.
5. Click Select to open the Atom Selection dialog box.
6. In the Molecule folder, choose Molecule Number from the list and enter `2` in the Molecule Number text box.
7. Click Add, then click OK.
8. In the Limit panel, click OK.

   The surface is extended to include molecule number 2.
9. In the Surface Table panel, click the Limit field for `MolSurf1` to remove the surface limit and redisplay the entire surface.

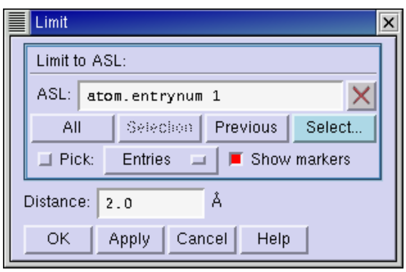
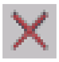


Figure 3.9. The* Limit *panel.

3.4.3 Generating a Surface for One Molecule in a Complex

An entry is frequently composed of multiple molecules, such as a co-crystallized receptor-ligand complex. Maestro is capable of generating a surface using a subset of atoms in the entry. In this example, you will use the `1err` entry to create a surface of just the atoms near the binding site, ignoring the ligand.

1. Choose Molecular Surface from the Surfaces submenu of the Display menu.
2. Enter `MolSurf2` in the Name text box.
3. Under Atoms for surface display, click the Clear button to clear the ASL text box.

4. Click Select to open the Atom Selection dialog box.
5. In the Molecule folder, select Molecule Number from the list on the left and enter `4` in the Molecule Number text box.
6. Click Add.
7. Click Proximity.

   The Proximity dialog box opens (see Figure 3.10).
8. Under Proximity, select Within and Angstroms, and enter `5.0` in the text box.
9. Under Fill, select Residues and select Exclude source.
10. Click OK in the Proximity dialog box and in the Atom Selection dialog box.
11. In the Molecular Surface panel, under Surface context, select Molecule.
12. Click Create Surface.

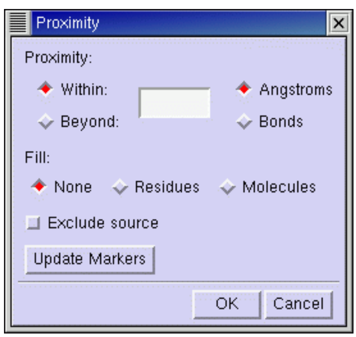


Figure 3.10. The Proximity ***dialog box.***

The resulting surface clearly defines the topology of the binding site.

13. Close the Molecular Surface panel.

    In the Surface Table panel, you can click Display Options and color the surface by partial charge or residue charge to visualize the electrostatics topology. You can also change the style or transparency to see the atoms under the surface. When you are finished, close the Display Options panel and the Surface Table panel.

14. Choose Undisplay All from the Surfaces submenu of the Display menu.

3.4.4 Creating a Site Map of the Binding Site

Maestro can be used to create site maps of receptors. The site map shows hydrophobic and hydrophilic regions, and is a tremendous asset when manually docking or adjusting ligands in a receptor. For this exercise, use the structure that was given the hydrogen treatment and map the region near the ligand. The atoms in the ligand do not need to be mapped, so they are excluded from the structure to map, but the ligand makes a logical center to place the bounding box.

1. Open the Project Table panel (Open/Close Project Table toolbar button, choose Show Table from the Project menu, or press CTRL+T).

2. Click the In field of the `1err_htreat` entry to display it in the Workspace.
3. Choose Sitemap (Hydrophobic/philic) from the Surfaces submenu of the Display menu.

   The Sitemap panel opens.

4. Select Workspace (included entries) from Use structures from.
5. Under Part of structure to map, click Select

   The Atom Selection dialog box opens.

6. In the Molecule folder, choose Molecule Number from the list on the left and enter `3` in the Molecule Number text box.
7. Click Add.
8. Click Proximity to open the Proximity dialog box.
9. Under Proximity, select Within and Angstroms, and enter `5.0` in the text box.

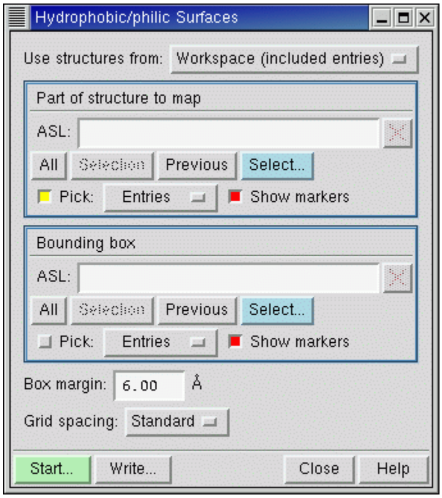


Figure 3.11. The* Sitemap *panel.

10. Under Fill, select Residues and select Exclude source.
11. Click OK in the Proximity dialog box and in the Atom Selection dialog box.
12. In the Sitemap panel, under Bounding box, choose Molecules from the Pick menu and select an atom in the ligand.
13. Enter `6.0` in the Box margin text box and choose Standard from the Grid Spacing option menu.
14. Click Start.

    The Start dialog box opens. You can keep the default settings.
15. Click Start to start the job.

    When the job finishes, the surface is displayed in the Workspace and the Surface Table panel is displayed.
16. Close the Monitor panel.
17. In the Surface Table panel, experiment with the transparency and the isovalue. For example, select the `philic` surface in the table and enter `-15.0` in the Isovalue text box at the bottom of the panel. Enter `-0.3` for the `phobic` isovalue.
18. When you are finished, close the Surface Table panel and the Sitemap panel.
19. Choose Close from the Project menu to close the project.

3.5 Creating and Manipulating Atom Sets

Defining subsets of atoms can be useful for many analysis and visualization tasks as well as for preparing MacroModel calculations. The Sets panel allows you to create and manipulate sets using the full range of atom selection tools. Once created, sets can be used in the Atom Selection dialog box or from relevant Pick menus. Sets are saved within a Maestro project. To use defined sets in another project, you can write them to a file using the Write button, then read them into the new project using the Read button.

These exercises use the all-atom protein-ligand complex in `1err.mae`:

1. Choose New from the Project menu and name the project `1errsets`.
2. Use the final structure produced in Section 3.3.11 on page 41 or import the structure from `1err_htreat.mae` from the `QuickTopics` directory. See Section 3.3.1 on page 31 for instructions on importing a structure.

3.5.1 Defining an Atom Set by Selecting Atoms

With the contents of `1err_htreat.mae` displayed in the Workspace, make a set that includes all atoms in the ligand:

Set 1: Ligand

1. From the Tools menu, choose Sets

   The Sets panel opens.

2. Click New (in the lower portion of the panel).

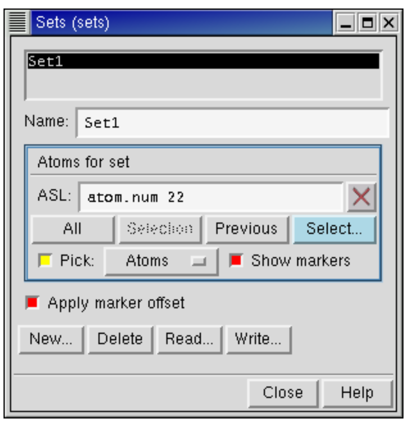


Figure 3.12. The* Sets *panel.

3. Enter `ligand` in the Set name text box, and click OK.

   A new set is created, named `ligand`.

4. In the Sets panel, under Atoms for set, select Show markers (see Figure 3.12).

5. Choose Molecules from the Pick menu.

6. In the Workspace, select an atom in the ligand to define the `ligand` set.

   If you need to identify the ligand, color the atoms by molecule number, or use the Find Atoms panel described on page 34. If you do use Find Atoms, deselect Mark found atoms once you have selected the desired atom.

Maestro highlights the atoms in the `ligand` set in green. Highlights are displayed as lines and dots, or as boxes, depending on the molecular representation of the atoms and bonds.

3.5.2 Defining an Atom Set with the Atom Selection Dialog Box

This exercise uses the Atom Selection dialog box to define more complex sets of atoms.

Set 2: Glycine residues

Create a set that contains all glycine residues in the structure:

1. Create a new set named `glycine`.

2. In the Sets panel, select Show markers.

3. Under Atoms for set, click Select.

   The Atom Selection dialog box opens.

4. In the Residue folder, select Residue Type from the list on the left, then select GLY from the Residue Type list in the center.

5. Click Add, then click OK.

You can switch between sets by selecting a set from the list at the top of the Sets panel.

Set 3: All residues with atoms within 5 Å of the ligand

Create a set containing the ligand and all atoms in complete residues within 5.0 Å of the ligand:

1. Create a new set named `lig+5A`.

2. In the Sets panel, under Atoms for set, click Select.

   The Atom Selection dialog box opens.

3. In the Set folder, select User-defined from the list on the left, then select `ligand` from the User-defined list in the center, and click Add.
4. Click the Proximity button.

   The Proximity dialog box opens.
5. Under Proximity, select Within and Angstroms, and enter `5.0` in the text box.
6. Under Fill, select Residues.
7. Click OK in the Proximity dialog box and in the Atom Selection dialog box.

   The `lig+5A` set is defined.

Set 4: Alpha carbons

Create a set of all the alpha-carbon atoms in the structure (atoms with a PDB atom type C-alpha):

1. Create a new set named `alphaC`.
2. Under Atoms for set, click Select.

   The Atom Selection dialog box opens.
3. In the Atom folder, select PDB type from the list on the left, then select CA from the PDB type list in the center.
4. Click Add, then click OK to define the `alphaC` set.

3.5.3 Defining Atom Sets With Boolean Operations

New sets can be created from existing sets using Boolean operations. If you do not already have the Sets panel displayed, open it from the Tools menu.

Set 5: NOT the ligand and NOT within 5 Å

Create a new set that contains all atoms that are neither in the ligand molecule nor within 5 Å of the ligand:

1. Create a new set named `frozen`.
2. Under Atoms for set, click Select.

   The Atom Selection dialog box opens.
3. In the Sets folder, select User-defined from the list on the left, then select `lig+5A` from the User-defined list in the center.

4. Click Subtract.
5. Click OK to define the `frozen` set.

This set could be used to specify those atoms to be fixed or frozen in a MacroModel calculation.

Set 6: The ligand and all the glycine residues

Create a set containing the atoms in the ligand and in the glycine residues:

1. Create a new set named `lig_or_gly`.
2. Under Atoms for set, click Select.

   The Atom Selection dialog box opens.
3. In the Sets folder, select User-defined from the list on the left, then select `ligand` from the User-defined list in the center.
4. Click Add.
5. In the Residue folder, select Residue Type from the list on the left, then select GLY from the Residue Type list in the center.
6. Click Add, then OK to define the `lig_or_gly` set.

Set 7: All glycine residues in the lig+5A set

Create a set containing only atoms in the glycine residues within the lig+5A set:

1. Create a new set named `lig_and_gly`.
2. Under Atoms for set, click Select.

   The Atom Selection dialog box opens.
3. In the Sets folder, select User-defined from the list on the left, then select `glycine` from the User-defined list in the center.
4. Click Add.
5. In the Sets folder, select User-defined from the list on the left, then select `lig+5A` from the User-defined list in the center.
6. Click Intersect, then OK to define the `lig_and_gly` set.

3.6 Current Energy Calculations

Many types of energetic calculations are available using MacroModel. This section introduces the MacroModel energetic panels and basic energetic parameters. These exercises calculate the current molecular mechanics energy of a structure in gas phase, then in solution phase.

Before starting the calculations, create a new project and import the substituted thymine structure from `Ecalc.mae`, from the `QuickTopics` directory. See Section 3.3.1 on page 31 for instructions on importing structures.

3.6.1 Calculating the Gas-phase Potential Energy

Determine the current gas-phase, molecular mechanics potential energy of the structure for a given force field:

1. Choose Current Energy from the MacroModel submenu of the Applications menu (see Figure 3.14 on page 54).
2. Choose Workspace (included entry) from the Use structures from option menu.
3. In the Potential folder, choose MMFFs from the Force Field option menu and choose None from the Solvent option menu.
4. In the ECalc folder, choose Complete from the Energy Listing option menu.
5. Click Start to open the Start dialog box (see Figure 3.13 on page 54).
6. Choose Replace existing entries from the Incorporate option menu.
7. Enter `Ecalc` in the Name text box.
8. Click Start to launch the job.

The energetic settings you selected instruct the Maestro job control facility to use the contents of the Workspace as input to perform a current energy calculation and to replace the entry corresponding to the Workspace with the structural results of the calculation. The settings also instruct Maestro to use the MMFFs force field, not to use a solution model (since this is a gas phase calculation), and to generate a complete listing of the molecular mechanics energy terms.

When you start the calculation, the Monitor panel opens, and text describing the job status is displayed in real time so that you can check the progress of the calculation. The job finishes quickly, and the results are incorporated into the project. Since you selected Replace existing entries, no new entries are added to the Project Table. Job files for this calculation are placed in your working directory or the directory you chose for output files. The detailed energy listing is written to a separate file, `Ecalc-out.mmo`.

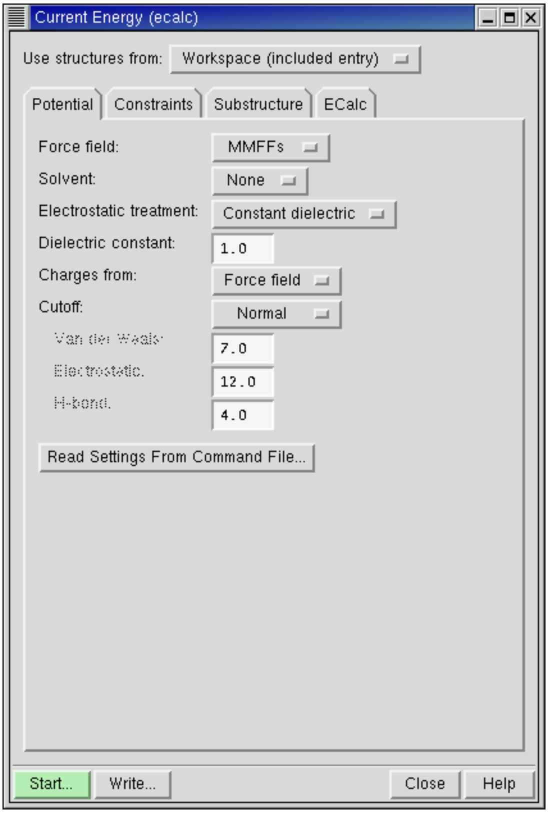


Figure 3.14. The Current Energy ***panel showing the*** Potential ***folder.***

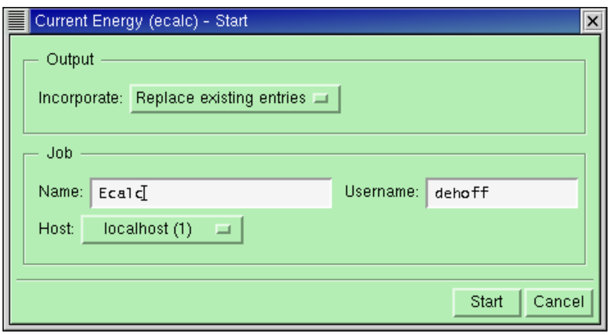


Figure 3.13. The Start ***dialog box for*** Current Energy***.***

3.6.2 Investigating Force Field Interactions

1. From the Tools menu, choose Force Field Viewer.
2. Click Browse, select `Ecalc-out.mmo` from the Files list, and click Open.
3. Click Stretch to open the Stretch panel (see Figure 3.15).
4. Click on a numbered pair in the list on the left to select a stretching interaction and display it in the Workspace with a magnifying glass icon.
5. To sort the stretching interactions, select Sort by Energy in the lower center portion of the panel.

   The list of stretching interactions is re-sorted so that the stretch with the lowest energy (that is, the least strained atom pair) is at the top of the list.
6. To investigate a particular stretching interaction, choose Bond from the Define Stretch pick menu and click on the desired bond in the Workspace.
7. To view stretching interactions by parameter quality, select the desired quality level from the Show option menu. View relevant force field parameters by clicking Show force field. This feature has limited utility for the BMFF force fields (MMFF and OPLS_2001).

The other panels opened from the Force Field Viewer panel are similar to the Stretch panel. You can experiment with bond angle, electrostatic, and other parameters.

8. When you are finished, close the Stretch panel and the Force Field Viewer.
9. Click the Clear Workspace button on the toolbar.

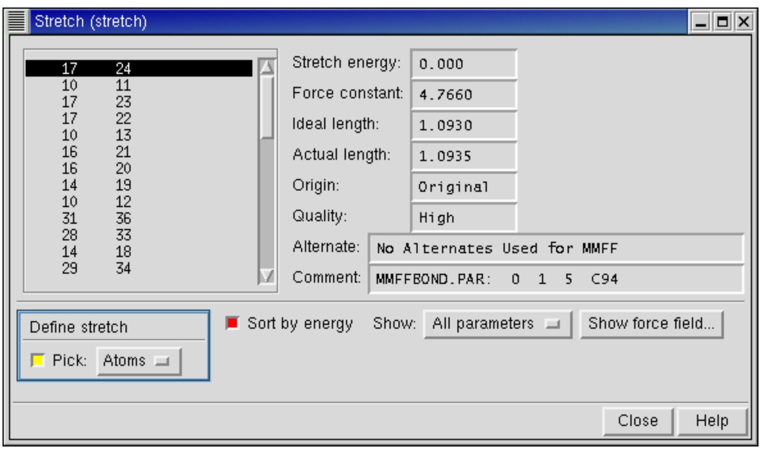


Figure 3.15. The Stretch ***panel.***

3.6.3 Calculating the Solution-phase Current Energy

1. Include Ecalc entry in the Workspace.
2. Choose Current Energy from the MacroModel submenu of the Applications menu.
3. Choose Workspace (included entry) from the Use structures from option menu.
4. In the Potential folder, choose MMFFs from the Force Field option menu, and choose Water from the Solvent option menu.
5. Enter 1.0 in the Dialectric constant text box.

   For all calculations using the GB/SA solvation model, the constant dielectric treatment is automatically used for the electrostatic part of the calculation. We recommend using a low molecular dielectric constant (for example, 1.0).
6. Click the ECalc tab and choose None from the Energy Listing option menu.
7. Click Start to open the Start dialog box.
8. Under Incorporate, select Append new entries.
9. In the Name text box, type EcalcSolv.
10. Click Start to launch the job.

Because you selected the Append new entries option, when the job finishes, a new entry is added to the Project Table with the total potential energy as a property. You can use the output in the Monitor panel or in the output Ecalc.log and EcalcSolv.log files to examine the details of the energies for the gas-phase and solution-phase calculations.

3.7 Energy Minimization

MacroModel energy minimizations are set up from the Minimization and Multiple Minimization panels within Maestro. Minimization calculations can be performed on single structures and multi-structure collections. In addition, for single structure calculations, the MacroModel substructure facility can be used to select fixed and frozen atoms for the minimization of a subset of atoms within a large structure.

For the next two exercises, you can either use the structure from Section 3.6.3 or create a new project and import Mini.mae from the QuickTopics directory. The entry title is Ecalc. See Section 3.3.1 on page 31 for instructions on importing structures.

3.7.1 Energy Minimization of a Single Structure

Minimize the structure using the default potential and minimization settings:

1. Choose Minimization from the MacroModel submenu of the Applications menu (see Figure 3.16).
2. Choose Workspace (included entry) from the Use structures from option menu.
3. Click Start to open the Start dialog box.
4. Under Incorporate, select Append new entries.
5. In the Name text box, type `Mini`.
6. Click Start to launch the job.

The Monitor panel is displayed. An intermediate structure is displayed in the Workspace with the atoms colored according to the energy gradient of the minimization at the time of monitoring. After job completion, the final minimized structure is incorporated into the project as a new entry. If you wish to change the default minimization setting, click the Mini tab.

Figure 3.16.** **The** Minimization **panel showing the** Mini **folder.

3.7.2 Comparing Structural Results: Superposition

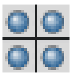
1. Click the Clear Workspace button in the toolbar.

2. Open the Project Table panel (Open/Close Project Table toolbar button, choose Show Table from the Project menu, or press CTRL+T).

3. Click the In column for the unminimized job input structure (first entry in the table).
4. Hold down the CTRL key and click the In column for the minimized output structure (second entry in the table).
5. Click the Tile entries button in the main window toolbar.

   A dialog box is displayed warning that the coordinates of the entries may change. Click Yes to proceed.

6. Choose Superposition from the Tools option menu.
7. Under Superimpose by ASL, click All to superimpose the structures (see Figure 3.17).
8. Close the Superposition panel.
9. Choose Close from the Project menu to close the project.

3.7.3 Energy Minimization of Multiple Structures

A collection of structures, either conformers or non-conformers, can be minimized in one computation using the Multiple Minimization panel.

1. Choose New from the Project menu and name the project `MultipleMin`.
2. Import the collection of structures in `MultMini.mae` from the `QuickTopics` directory using the steps outlined in Section 3.3.1 on page 31.

   Select Import All Structures in the Import panel. This file contains 10 small molecular structures.

3. Open the Project Table panel (Open/Close Project Table toolbar button, choose Show Table from the Project menu, or press CTRL+T).

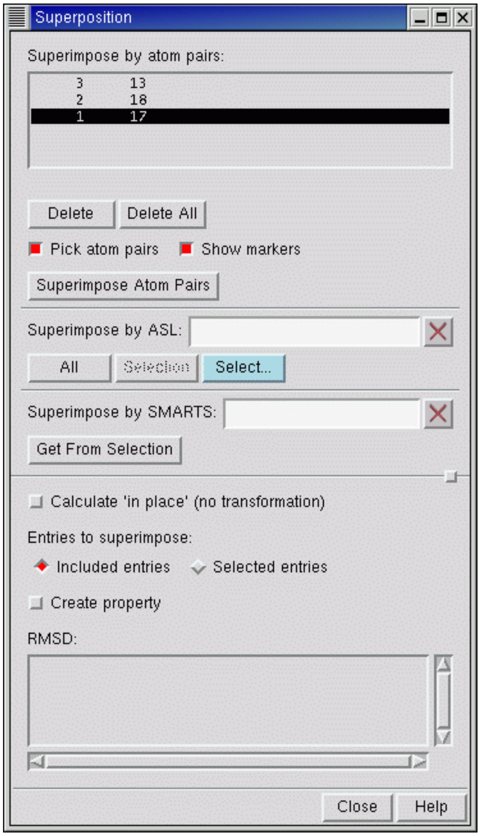


Figure 3.17. The Superposition ***panel.***

4. Select all 10 structures in the Project Table. See Section 2.4 on page 11 for information on selecting entries.
5. Choose Multiple Minimization from the MacroModel submenu of the Applications menu.
6. Choose Project Table (selected entries) from the Use structures from option menu (see Figure 3.18).
7. Click Start to open the Start dialog box.
8. Under Incorporate, select Replace existing entries.
9. In the Name text box, type `MultMini`.
10. Click Start to launch the job.

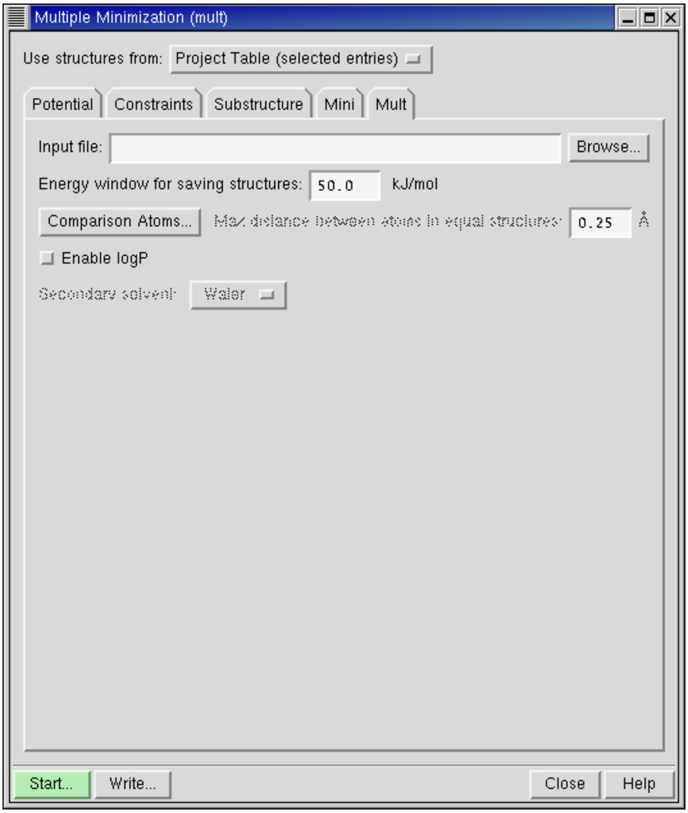


Figure 3.18. The Multiple Minimization ***panel showing the*** Mult ***folder.***

This computation uses the selected entries as the input structure file and replaces the input entries in the Project Table with the resulting energy minimized structures at the conclusion of the calculation.

For multi-conformer computations, you can eliminate duplicate minima and reduce the output by using the tools in the Mult folder of the Multiple Minimization panel to define an energetic window and identify comparison atoms.

11. Choose Close from the Project menu to close the project.

3.7.4 Energy Minimization of a Substructure

The time required to minimize large structures can be drastically reduced by focusing on a particularly important section of the structure and restraining, freezing, or ignoring the rest. This exercise uses the protein-ligand complex from Section 3.3 to perform a substructure minimization. The ligand and all residues within 5.0 Å of the ligand are freely minimized. The atoms between 5.0 Å and 10.0 Å from the ligand are restrained, while the atoms between 10.0 Å and 15.0 Å from the ligand are frozen. The remaining atoms are ignored. For more information on the Substructure facility, see Section 5.3.3 of the *MacroModel User Manual*.

1. Click on the Clear Workspace button on the toolbar.
2. Create a new project and import the structure in `SubsMini.mae` from the `QuickTopics` directory, using the directions in Section 3.3.1 on page 31.

   The ligand in this complex is molecule number 3.
3. Choose Minimization from the MacroModel submenu of the Applications menu.
4. Choose Workspace (included entry) from the Use structures from option menu.
5. In the Potential folder, choose OPLS_2001 from the Force field option menu.
6. In the Mini folder, enter `5000` in the Maximum iterations text box.
7. Create a new set named `lig+5A`.
   a. From the Tools menu, choose Sets.

      The Sets panel opens.

   b. Click New (in the lower portion of the panel).
   c. Enter `lig+5A` in the Set name text box, and click OK.

      A new set is created, named `lig+5A`.

   d. In the Sets panel, under Atoms for set, select Show Markers.
   e. Choose Molecules from the Pick menu.
   f. In the Workspace, select an atom in the ligand.

      If you need to identify the ligand, color the atoms by molecule number, or use the Find Atoms panel described on page 34. If you do use Find Atoms, deselect Mark found atoms once you have selected the desired atom.

   g. In the Sets panel, under Atoms for set, click Select.

      The Atom Selection dialog box opens.

   h. In the Molecule folder, click the Proximity button.

      The Proximity dialog box opens.

   i. Under Proximity, select Within and Angstroms, and enter `5.0` in the text box.
   j. Under Fill, select Residues.

k. Click OK in the Proximity dialog box and in the Atom Selection dialog box.

   The `lig+5A` set is defined.

8. In the Minimization panel, click the Substructure tab (see Figure 3.19).
9. Under Atoms for substructure, click Select.

   The Atom Selection dialog box opens.

10. In the Set folder, select User-defined from the list on the left, then select `lig+5A` from the User-defined list in the center.
11. Click Add, then click OK.
12. Select Show markers to highlight the atoms in the substructure.

    This is the section of the structure that is minimized without restraints.

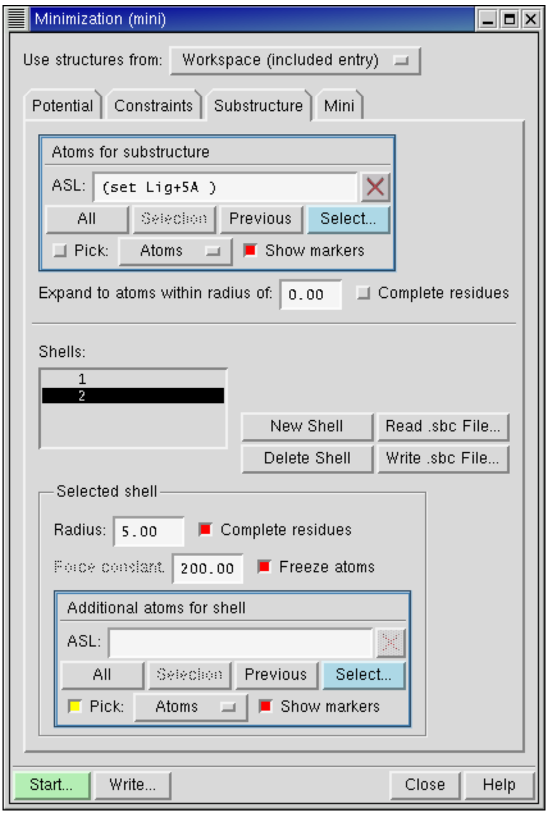


Figure 3.19. The** Minimization **panel showing the** Substructure **folder.

Next, you will define a shell of restrained atoms and another shell of frozen atoms.

13. Click New Shell in the middle part of the Substructure folder.
14. Under Selected shell, select Complete residues.
15. Enter `5.0` in the Radius text box.

    The restrained atoms are highlighted in orange in the Workspace.
16. Click New Shell again.
17. Under Selected shell, select Complete residues and Freeze Atoms.
18. Enter `5.0` in the Radius text box.

    The frozen atoms are labeled in purple in the Workspace.
19. Click Start.
20. Choose Append new entries from the Incorporate option menu.
21. Enter `SubsMini` in the Name text box.
22. Click Start to launch the job.

    This job may take several minutes to finish.
23. When you are finished, choose Close from the Project menu to close the project.

3.8 Conformational Searching with MacroModel

The goal of conformational searching is to locate the low-energy configurations of a molecular structure. MacroModel includes a number of conformational searching algorithms as well as mixed methods. This exercise first explores three standard conformational searches, then explores searches with the ligand/protein system prepared earlier. The first three searches are:

- Monte Carlo Multiple Minimum (MCMM), which generates trial conformations by randomly adjusting rotatable bonds.
- Serial MCMM conformational searches, which enable multiple non-conformers to be used as input to a single MCMM run
- Low-mode searching, which explores the low-frequency eigenvectors of the system to generate new conformations.

3.8.1 Performing an MCMM Search

1. Create a new project and import `MCMM.mae` from the `QuickTopics` directory, using the directions in Section 3.3.1 on page 31.
2. Choose Conformational Search from the MacroModel submenu of the Applications menu.
3. Choose Workspace (included entries) from the Use structures from option menu (see Figure 3.20 on page 65).
4. In the Substructure folder, click the Clear button in both the Atoms for substructure section and in the Shells section, to clear any previously defined substructures and shells.
5. In the Shells section, click Delete Shells until all shells are deleted.
6. In the CSearch folder, choose Torsional sampling (MCMM) from the Method option menu.
7. Enter `200` in the Maximum number of steps text box.
8. Click the Perform Automatic Setup button.

   The parameters of the calculation should be displayed as markers on the structure. If they are not, click the Display All Markers button in the Search Variables section. Many of the variables define conformational comparisons, which govern how the generated structures are compared and duplicates eliminated. They can be individually examined from the parameter panels, which you open by clicking the respective parameter buttons in the center of the folder. The defaults are sufficient for this exercise.

9. Click Start to open the Start dialog box.
10. Choose Append new entries from the Incorporate option menu.
11. Enter `MCMM` in the Name text box.
12. Click Start to launch the job.

    This calculation takes a couple of minutes to finish. The Workspace is updated with the current low-energy structure during the calculation.

The output structure file, `MCMM-out.mae`, contains all structures found within the specified energetic window. The output log file, `MCMM.log`, includes a convenient listing of the molecular mechanics potential energy of all the output structures.

13. When you have finished, choose Close from the Project menu.

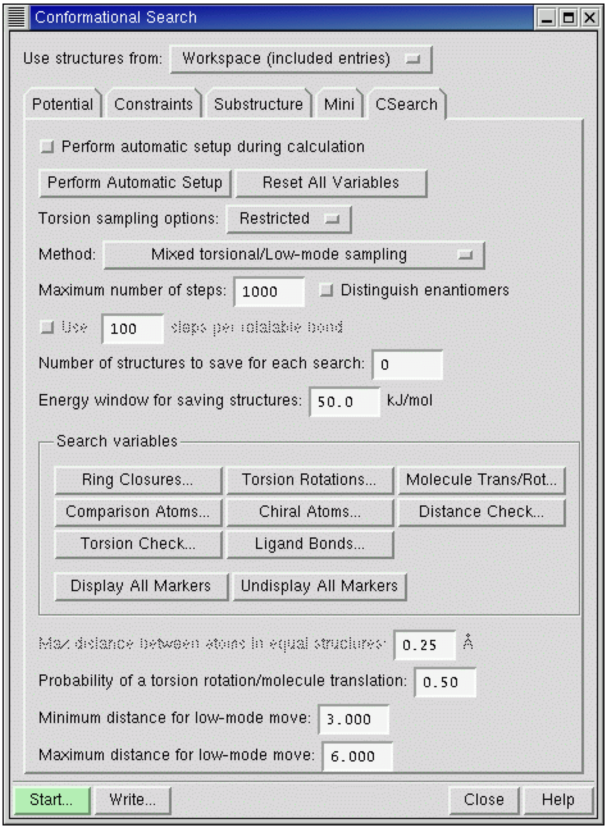


Figure 3.20. The Conformational Search ***panel showing the*** CSearch ***folder.***

3.8.2 Performing a Serial MCMM Conformational Search

Serial MCMM conformational searches perform an MCMM conformation search on each input structure, with MCMM parameters that are set up automatically (by means of an `AUTO` opcode in the command file).

1. Create a new project and import `Serial.mae` from the `QuickTopics` directory, using the directions in Section 3.3.1 on page 31.
2. In the Project Table, select the three imported entries.
3. Choose Conformational Search from the MacroModel submenu of the Applications menu.
4. Choose Project Table (selected entries) from the Use structures from option menu.

5. In the CSearch folder, choose Serial torsional sampling (MCMM) from the Method option menu.

   Perform automatic setup during calculation (at the top of the panel) is automatically selected and dimmed because it is mandatory for this type of calculation.

6. Enter `100` in the Number of steps text box.
7. Click Start to open the Start dialog box.
8. Choose Append new entries from the Incorporate option menu.
9. Enter `SerialMCMM` in the Name text box.
10. Click Start to launch the job.

    The output structures are incorporated into the Project Table when the conformational search is finished.

The `serial_split` utility can be used to divide the results of a serial search into individual output files for the individual input structures. See Section 20.7 of the *MacroModel User Manual* for more information.

3.8.3 Performing a Serial Low-Mode Search

A low-mode calculation does not require the designation of ring structures and variable torsion angles.

1. Use the structure set from the previous multiple minimization (see Section 3.7.3 on page 58) or import `Serial.mae` from the `QuickTopics` directory.
2. In the Project Table, select three entries.
3. Choose Conformational Search from the MacroModel submenu of the Applications menu.
4. Choose Project Table (selected entries) from the Use structures from option menu.
5. In the CSearch folder, choose Serial low-mode sampling from the Method option menu.
6. Enter `100` in the Number of steps text box.
7. Click Start to open the Start dialog box.
8. Choose Do not incorporate from the Incorporate option menu.
9. Enter `SerialLMOD` in the Name text box.
10. Click Start to launch the job.

The output structure file, `SerialLMOD-out.mae`, contains a collection of minimized configurations for each input structure.

11. When you have finished, choose Close from the Project menu to close the project.

3.8.4 Fast, Broad Conformer Generation Using ConfGen

The ConfGen utility is a new conformation search facility that rapidly and systematically generates a broad collection of diverse conformations for ligand-sized input structures. This contrasts with other more exhaustive, yet slower, search utilities available in MacroModel. ConfGen efficiently generates compact collections of quality candidate structures.

1. Create a new project and import the structure in `Serial.mae` from the `QuickTopics` directory, using the directions in Section 3.3.1 on page 31.

   This file contains three different sample structures. The entries corresponding to these structures are automatically selected in the Project Table.

2. Choose Ligand Torsion Search from the MacroModel submenu of the Applications menu.
3. Choose Project table (selected entries) from the Use structures from option menu.
4. In the Potential folder, select the appropriate energetic settings.

   For this example, the default settings are acceptable, although GB/SA water solvation and distance-dependent dielectric are recommended for ConfGen searches. See the *MacroModel User Manual* and the *MacroModel Reference Manual* for more information.

5. In the Mini folder, select the minimization settings.

   It is important that the bond lengths and bond angles be optimized by minimization before commencing a ConfGen search. The minimization of ConfGen-generated conformations is controlled by the Post-minimization of generated structures text box. This minimization step is the most resource-intensive portion of the workflow, and may not be needed for all applications.

6. In the LTSearch folder, select the desired search variables and redundant conformer elimination parameters (see Figure 3.21).

   The Number of search moves indicates the number of conformers that are passed on to undergo post-ConfGen MacroModel minimization and processing. This conformer set represents a uniform subset of the total ConfGen-generated pool of conformers.

   You can reduce the final set of output conformations, based on relative energy, by selecting Save at most *n* conformations per ligand. This is the final set after minimization and redundant conformer elimination.

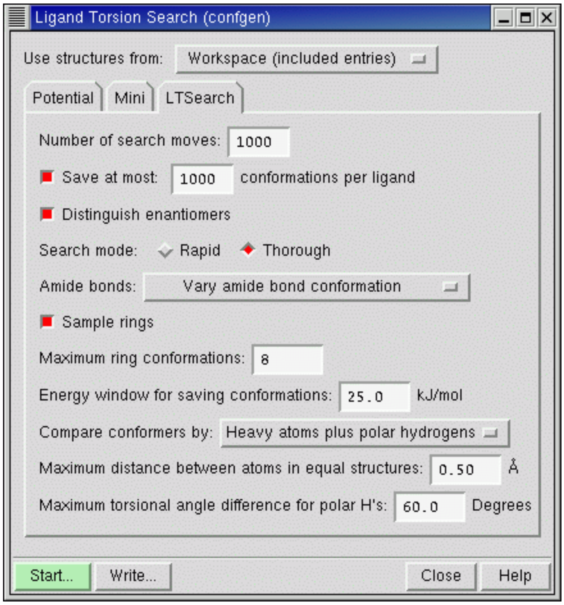


Figure 3.21. The* Ligand Torsion Search *panel showing the* LTSearch *folder.

7. Select the appropriate Search mode setting for sampling about the terminal rotatable bonds.
8. Select from the optional search features including amide bond sampling, ring sampling, and energy window for saved conformers.

   Redundant conformer elimination settings are found at the bottom of the panel. The default settings are appropriate for this exercise.
9. Click Start
10. In the Start dialog box, choose Append new entries from the Incorporate option menu.
11. In the Name text box, type `FastConf`.
12. Click Start to launch the job.

    After the search is complete, the generated structures, with properties, are placed in the Project Table for further analysis.
13. When you have finished, choose Close from the Project menu to close the project.

3.8.5 Ligand Conformational Search with a Frozen Receptor

In Section 3.7.4, a protein-ligand complex was minimized using the OPLS_2001 force field. There are multiple approaches to performing a subsequent conformational search on the complex. Two methods are demonstrated in the following two sections.

This first exercise demonstrates how to perform a substructure conformational search on the protein/ligand complex from Section 3.5.3 on page 51, keeping the protein frozen. The MCMM method is used for the ligand.

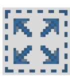
To set up the job:

1. Import the minimized structure `LigandMCMM.mae` from the `QuickTopics` directory, or use the protein-ligand complex from the previous exercise.
2. Display the structure in the Workspace.
3. Choose Conformational Search from the MacroModel submenu of the Applications menu.
4. Choose Workspace (included entries) from the Use structures from option menu.
5. In the Potential folder, choose OPLS_2005 from the Force field option menu and choose None from the Solvent option menu.
6. In the CSearch folder, choose Torsional sampling (MCMM) from the Method option menu.
7. For a shorter computation, enter `200` in the Maximum number of steps text box.

To set conformational search parameters manually for the ligand:

Note that this setup would not be adequate for a complete search of conformational space.

1. Display only the ligand molecule (see Section 3.3.6 on page 36 for instructions).
2. Center the ligand in the Workspace by right-clicking on a central atom in the ligand.
3. Click the Fit to screen button on the main toolbar.



4. In the Conformational Search panel, click the CSearch tab, then click Reset All Variables.
5. Click Comparison Atoms (located in the middle of the panel) to open the Comparison Atoms panel (see Figure 3.22 on page 70).

The procedure below selects the non-hydrogen atoms of the ligand.

6. Under Define comparison atoms, click Select to open the Atom Selection dialog box.

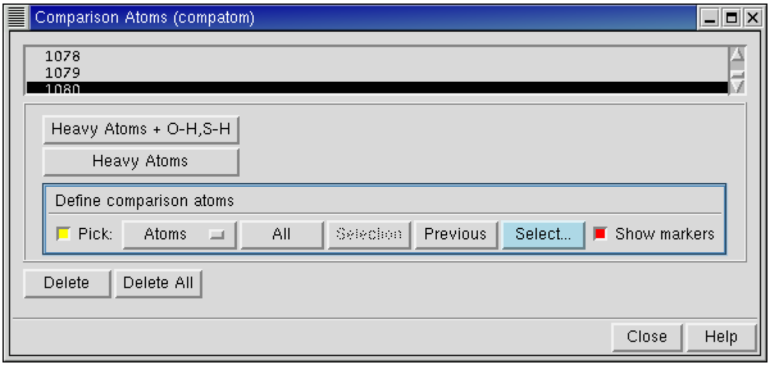


Figure 3.22. The Comparison Atoms ***panel.***

7. In the Molecule folder, select Molecule Number from the list and type `4` in the Molecule Number text box (or click on the molecule in the Workspace), then click Add.

8. In the Atom folder, select Element from the list on the left, then select H from the Element list, and click Subtract to remove the hydrogen atoms from the selection set.

9. Click OK, then close the Comparison Atoms panel.

10. In the CSearch folder, click the Torsion Rotations button to open the Torsion Rotations panel (see Figure 3.23).

    Torsion rotations indicate the torsions that are randomly rotated during the search. All non-trivial C-C and N-C bonds (except amide torsions) could be selected. It is only necessary to choose the second and third atoms of the torsion.

11. Choose Atoms from the Pick menu and select a few torsions from the structure in the Workspace, (e.g., 1770/1771, 1779/1780, 1789/1790).

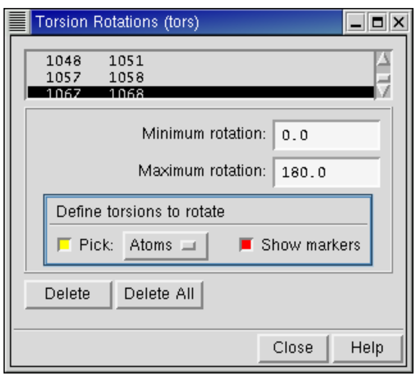


Figure 3.23. The Torsion Rotations ***panel.***

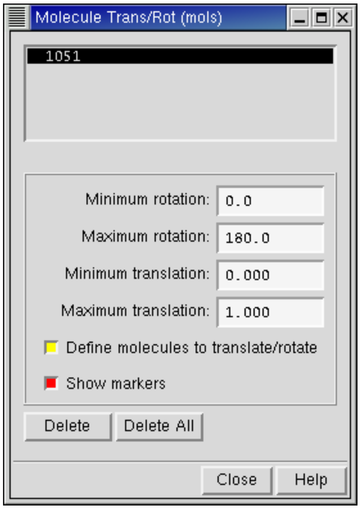


Figure 3.24. The Molecule Trans/Rot ***panel.***

12. Close the Torsion Rotations panel.
13. In the CSearch folder, click the Molecule Trans/Rot button to open the Molecule Trans/Rot panel (see Figure 3.24).

    The Molecule Trans/Rotation feature identifies molecules that are to be rotated and translated relative to each other. Only the ligand needs to be specified in this example.
14. In the Workspace, select any atom in the ligand. Use the default minimum and maximum values.
15. Close the Molecule Trans/Rot panel.

To freeze the protein and start the job:

This section uses the Substructure facility to freeze the receptor atoms that are within 6 Å of the ligand.

1. Redisplay all atoms by choosing All from the Also display button menu on the main toolbar.

   
2. In the Substructure folder of the CSearch panel, click the Clear button in both the Atoms for substructure section and in the Shells section, to clear any previously defined substructures and shells.

3. In the ASL text box of the Atoms for substructure section, enter:

   `mol.n 4`

4. In the Shells section, click Delete Shells until all shells are deleted, then click New Shell.
5. Select Complete residues and enter `6.0` in the Radius text box.
6. Select Freeze atoms.

Maestro colors the frozen atoms orange; the remainder are ignored in the computation.

7. Click Start.
8. In the Start dialog box, choose Append new entries from the Incorporate option menu.
9. Enter `LigandMCMM` in the Name text box.
10. Click Start to launch the job.

    This computation will take one to three hours, depending on your computer.

11. When the calculation is complete, import the output structure file `LigandMCMM-out.mae` and select the entries.
12. Use the ePlayer to view the different low-energy orientations.

    See Section 2.4.1 on page 13 for a description of the ePlayer. For more information, see Section 8.6 of the *Maestro User Manual*.

13. When you have finished, choose Close from the Project menu to close the project.

3.8.6 Substructure Conformational Search with Automatic Setup

The last exercise demonstrated a computation in which the ligand was manually assigned Monte Carlo conformational search parameters while the entire receptor was held frozen. This exercise demonstrates a modified conformational search that enables increased receptor flexibility, using Perform Automatic Setup to define the MCMM search variables.

The steps below prepare a substructure conformational search calculation in which the receptor is divided into freely moving, fixed, and frozen regions. Computations using substructures use less resources than full receptor simulations. Automatic Setup recognizes substructures and assigns the MCMM conformational search parameters only to functional groups in the substructure, and not to those in the restrained or frozen part of the structure.

To set up the job:

1. Create a new project and import the structure in `SubsAuto.mae` from the `QuickTopics` directory, using the directions in Section 3.3.1 on page 31.

2. Display the structure in the Workspace.
3. Choose Conformational Search from the MacroModel submenu of the Applications menu.
4. Choose Workspace (included entries) from the Use structures from option menu.
5. In the Potential folder, choose OPLS_2001 from the Force field option menu and choose None from the Solvent option menu.
6. In the Mini folder, enter `5000` in the Maximum iterations text box.
7. In the CSearch folder, choose Torsional sampling (MCMM) from the Method menu and click Reset All Variables. For a shorter computation, change the value in the Number of steps text box to `200`.

To set up the substructure and shells that define moving, fixed, and frozen atoms:

In this example, the freely-moving portion includes the ligand, as well as all residues within 3 Å of the ligand.

1. Click the Substructure tab.
2. Under Atoms for substructure, choose Molecules from the Pick menu and click on an atom in the ligand in the Workspace.
3. Enter `3.0` in the Expand to atoms within radius of text box.

   You could achieve the same result by using the Atom Selection dialog box to select molecule number 4 and the atoms within 3 Å, or by entering the following expression in the ASL text box:

   ```
   fillres within 3 (mol.num 4)
   ```
4. Select Complete residues.
5. Click New Shell.
6. Under Shells, select Complete residues and enter `2.0` in the Radius text box.

   This is the shell of fixed atoms, with harmonic constraints of 200 kJ/mol Å^2 applied.
7. Click New Shell.
8. Under Shells, select Complete residues and Freeze atoms and enter `2.0` in the Radius text box.

   This is the shell of frozen atoms.

The moving, fixed, and frozen regions have now been defined and are indicated in the Workspace as white, orange, and purple regions.

9. Use the automatic setup features to define the MCMM conformational search variables. You can set up variables either for the entire moving region (the substructure) or only for the ligand molecule. Atoms in the fixed or frozen atom regions do not have conformational search variables assigned to them when using Perform Automatic Setup. Do one of the following:
   - Click the CSearch tab and click Perform Automatic Setup to assign MCMM parameters to the entire freely-moving region.
   - Enter the following command in the command input area of the main window to assign MCMM parameters to the ligand only:

     ```
     autosetup mol.n 3
     ```

To enter the job information and start the job:

1. Click Start.
2. In the Start dialog box, choose Append new entries from the Incorporate option menu.
3. Enter `SubsAuto` in the Name text box.
4. Click Start to launch the job.

The sample files included in the distribution have conformational search variables defined only for the ligand.

5. When you have finished, choose Close from the Project menu to close the project.

3.9 Large-Scale Low-Mode Conformational Search

The large-scale low-mode (LLMOD) conformational searching routine is a unique method for generating candidate conformations of very large structures, including full proteins. Combinations of low-frequency vibrational modes are used to produce candidate structures. These modes represent simultaneous, concerted conformational changes in the structure.

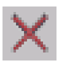
Specialized applications of LLMOD include protein loop optimization, homology model refinement, and fully flexible docking for induced-fit modeling. In addition, LLMOD-generated conformations can be used for subsequent rigid docking studies.

If you are not continuing from the previous exercise, start Maestro and either open an existing project or save the current scratch project as a named project.

For this exercise, you will use the crambin structure 1crn, which is contained in the file `LLMOD.mae` in the `QuickTopics` directory. This is a 14-amino acid sequence. Large proteins can take multiple hours to complete the LLMOD conformational search. Solvation should generally be used for LLMOD searches, but it is not used in this exercise in order to speed the computation.

The example structure has been minimized with OPLS_2001 without solvation. Any structure used in an LLMOD conformational search must be initially minimized to a low gradient with the same force field and solvation treatment that will be used in the conformational search.

1. Create a new project and import the the protein in `LLMOD.mae` from the `QuickTopics` directory, using the directions in Section 3.3.1 on page 31.
2. Choose Conformational Search, from the MacroModel submenu of the Applications menu.
3. Choose Workspace (included entries) from the Use structures from option menu.
4. In the Potential folder, choose OPLS_2001 from the Force field option menu.
5. In the Constraints folder, clear any previously set constraints by clicking Reset All in both the Constrain section and the Freeze section.
6. In the Substructure folder, click the Clear button in both the Atoms for substructure section and in the Shells section, to clear any previously defined substructures and shells.

7. In the Shells section, click Delete Shells until all shells are deleted.
8. In the CSearch folder, select Large scale low-mode sampling from the Method option menu.

   A Conformation dialog box prompts you to change the convergence criteria. Click OK.

9. Enter `100` in the Number of steps text box.
10. In the Mini folder, enter `1.00` in the Convergence threshold text box.
11. Click Start to open the Start dialog box.
12. Choose Append new entries from the Incorporate option menu.
13. Enter `LLMOD` in the Name text box.

After the job finishes, Maestro incorporates the structures into the Project Table. Depending on the size of the structure, the computation may take some time to complete.

14. When you have finished, choose Close from the Project menu to close the project.

3.10 eMBrAcE

eMBrAcE is an automated routine that uses a collection of individual ligands, each pre-positioned with respect to a given receptor. eMBrAcE automatically performs energetic calculations on each complex formed from the receptor and the individual ligands. eMBrAcE can work in two modes—interaction mode and energy difference mode. In the first, the receptor and the ligand are individually treated as separate sets, and only the energy components between sets are evaluated and recorded. The eMBrAcE energy difference mode reports the minimized energy of both the individual ligand and receptor subtracted from the minimized energy of the complex. It is also possible to perform eMBrAcE calculations using conformational searches.

eMBrAcE calculations can be accelerated by using substructures with constraints applied to atom positions. The substructure need only include elements of the protein, not any ligands. This exercise demonstrates how to import a receptor and a group of ligands, and import a substructure and run the calculations with constraints.

If you are not continuing from the previous exercise, start Maestro and either open an existing project or save the current scratch project as a named project.

1. Create a new project and import `eMBrAcE.mae` from the `QuickTopics` directory, using the directions in Section 3.3.1 on page 31.

   This file contains a single protein and four pre-positioned ligands. Only the first structure, the receptor, is displayed in the Workspace.

2. In the Project Table, select all of the entries.

   The structural input to an eMBrAcE calculation must contain the receptor first, followed by the pre-positioned ligands. In Maestro, the receptor must be the first selected entry.

3. Choose eMBrAcE Minimization from the MacroModel submenu of the Applications menu.
4. In the Potential folder, choose OPLS_2001 from the Force field option menu.
5. In the Mini folder, enter `1000` in the Maximum Iterations text box.
6. Click the eMBrAcE tab (see Figure 3.25).
7. Under Source of ligands, select Selected entries.
8. Under Receptor, select First selected entry.
9. Under Association energy mode, select Interaction energy mode.
10. Under Structures saved, select Complexes only.

11. In the Substructure folder, click the Read .sbc file button in the lower right corner of the panel and select `eMBrAcE.sbc` from the `QuickTopics` directory.

    The atoms in the structure are highlighted: white markers for the substructure, orange markers for shell 1, and purple markers for shell 2.

12. Click Start to open the Start dialog box.
13. Choose Append new entries from the Incorporate option menu.
14. Enter `eMBrAcE` in the Name text box.
15. Click Start to launch the job.

This calculation may take 10 minutes. When the calculation is complete, the results are placed in a table at the end of the `eMBrAcE.log` file and are incorporated into the Project Table.

16. When you have finished, choose Close from the Project menu to close the project.

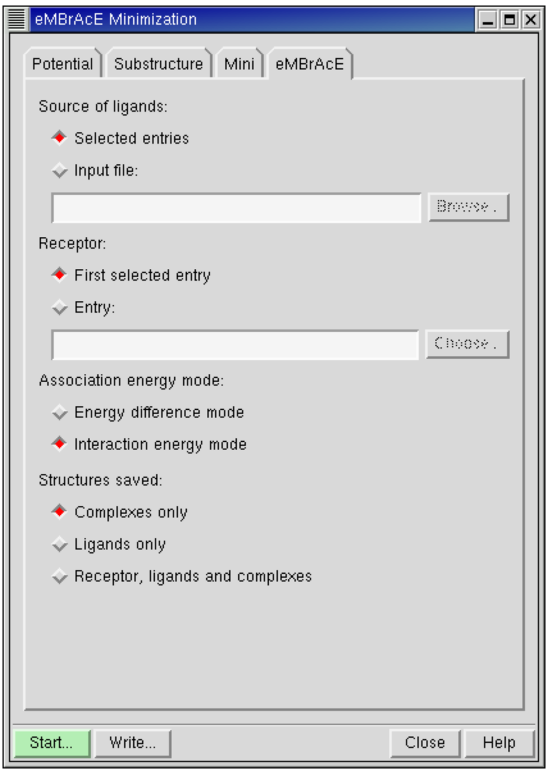


Figure 3.25. The eMBrAcE Minimization ***panel showing the*** eMBrAcE ***folder.***

3.11 Molecular Dynamics with MacroModel

Molecular dynamics calculations simulate molecular movement over time using Newton's equations of motion. In this exercise, you will run an MC/SD dynamics calculation.

In the MC/SD simulation, an initial minimization is performed to ensure that the structure is at a minimum on the potential energy surface. Geometric structural parameters can be monitored over the course of the dynamics simulation, and structures can be sampled during the simulation at constant intervals. Since MC/SD uses Monte Carlo methods, it is also necessary to define the Monte Carlo parameters.

1. Create a new project and import the structure in `MCSD.mae` from the `QuickTopics` directory, using the directions in Section 3.3.1 on page 31.

   This structure has been minimized to a low gradient with MMFFs in the gas phase.

2. Choose MC/SD from the MacroModel submenu of the Applications menu.

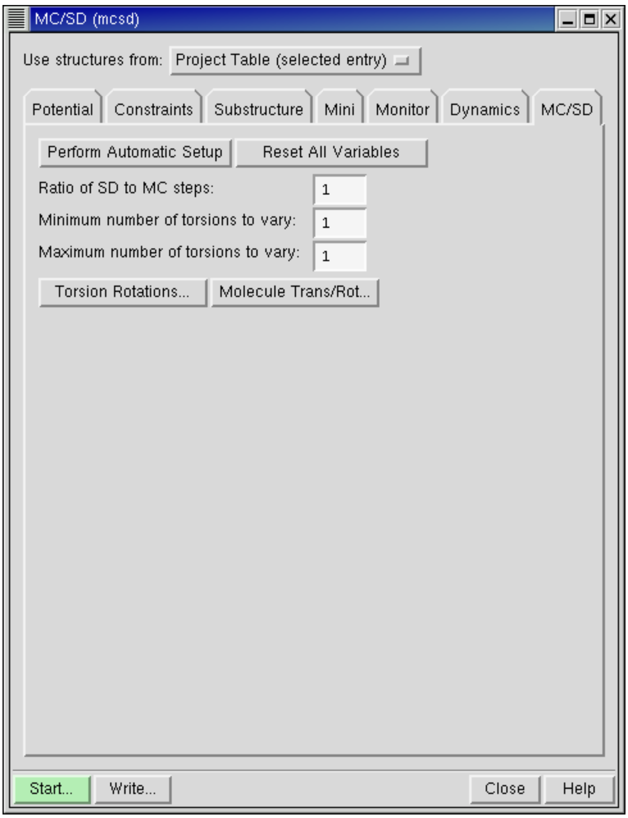


Figure 3.26. The* MC/SD *panel showing the* MC/SD *folder.

3. Choose Workspace (included entry) from the Use structures from option menu.
4. In the Potential folder, choose MMFFs from the Force field option menu and choose None from the Solvent option menu.
5. In the Constraints folder, clear any previously set constraints by clicking the Reset All button in both the Constrain section and the Freeze section.
6. In the Substructure folder, click the Clear button in both the Atoms for substructure section and in the Shells section, to clear any previously defined substructures and shells.
7. In the Shells section, click Delete Shells until all shells are deleted.
8. In the Mini folder, enter `5000` in the Maximum iterations text box and enter `0.002` in the Convergence threshold text box.

   These parameters are required for the initial minimization.
9. In the Monitor folder, enter `10` in the Number of structures to sample text box.

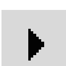
   You can use the buttons in this folder if you want to conduct additional structural monitoring.
10. In the Dynamics folder, choose Stochastic dynamics from the Method option menu, and choose Nothing from the SHAKE option menu.

    SHAKE is not recommended for MC/SD simulations.
11. In the MCSD folder, click Perform Automatic Setup (see Figure 3.26 on page 78).

    To view the selected torsions, click Torsion Rotations in the middle of the panel.
12. Click Start to open the Start dialog box.
13. Choose Append new entries from the Incorporate option menu.
14. Enter `MCSD` in the Name text box.
15. Click Start to launch the job.

    The ten sampled structures are incorporated into the Project Table at the completion of the computation.

After incorporation, you can view the sample trajectory using Maestro's ePlayer. The incorporated structures should already be selected in the Project Table. Click the Play forward button in the Project Table toolbar to view the trajectory in the Workspace.



See Section 2.4.1 on page 13 for a description of the ePlayer. For more information, see Section 8.6 of the *Maestro User Manual*.

16. When you have finished, choose Close from the Project menu to close the project.

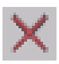
3.12 Creating Energy Profiles From Dihedral Drives

A contour diagram describing the molecular mechanics potential energy of a structure, relative to the value of either one or two dihedral angles, can be generated with MacroModel. These exercises demonstrate how to produce a contour diagram describing the variation in energy of a molecule with respect to rotation of two dihedral angles.

3.12.1 Performing a Dihedral Drive Computation

For this exercise, you can use the same structure as in Section 3.6 on page 53, import the structure in `Ddrive.mae` from the `QuickTopics` directory, or build your own structure with at least two non-trivial torsion angles.

1. Create a new project and display the structure in the Workspace.
2. Choose Dihedral Drive from the MacroModel submenu of the Applications menu.
3. Choose Workspace (included entry) from the Use structures from option menu.
4. In the Potential folder, choose MMFFs from the Force Field menu and choose None from the Solvent option menu.
5. In the Substructure folder, click the Clear button to clear any substructure.



6. Click Delete Shell enough times to clear all shells.
7. Label all atoms in the structure by atom number. See Section 3.3.7 on page 38 for instructions on labeling.
8. In the Drive folder, under Define dihedral to drive, choose Atoms from the Pick menu (see Figure 3.27).
9. In the order listed, pick the atoms in the Workspace that define the two angles: 1, 14, 15, 16, and 6, 25, 26, 27. (Use the middle mouse button to rotate the structure, if necessary.)
10. Click Start to open the Start dialog box.
11. Choose Do not incorporate from the Incorporate option menu.
12. Enter `Ddrive` in the Name text box.

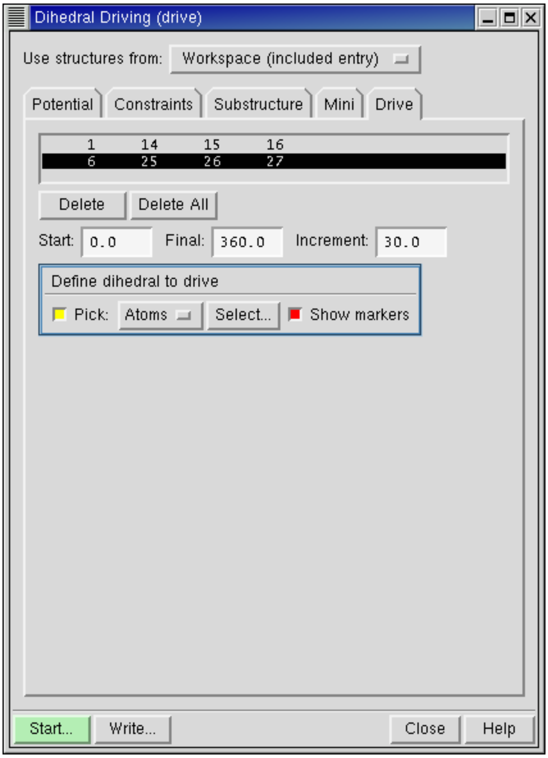


Figure 3.27. The* Dihedral Drive *panel showing the* Drive *folder.

13. Click Start to launch the job.

    Two files are produced:

    - `Ddrive-out.grd` contains the energetic results of the calculation
    - `Ddrive-out.mae` contains the structural output.

3.12.2 Analyzing the Results of the Dihedral Drive

You can create a contour diagram by reading `Ddrive-out.grd` from the 2D Plot panel (see Figure 3.28):

1. From the Tools menu, choose 2DPlot.
2. Click Open and select `Ddrive-out.grd` from your working directory, or from the `QuickTopics` directory
3. Click Open.

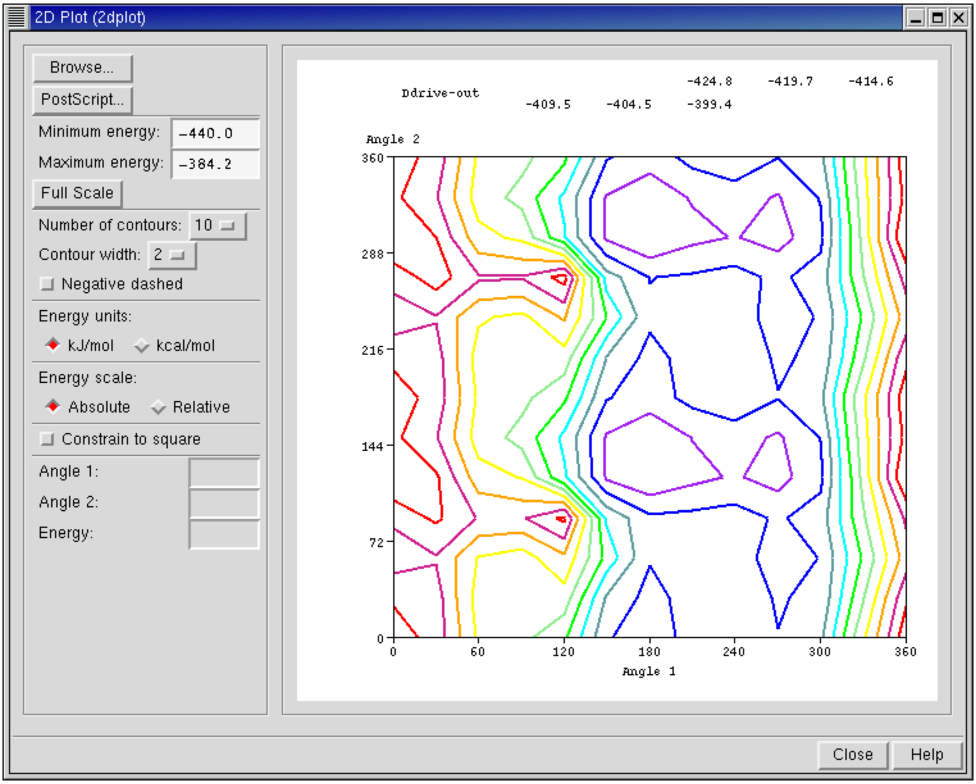


Figure 3.28. The 2D Plot ***panel.***

The interactive plot opens and the output structure file is imported into the project and displayed in the Workspace. When you press the middle mouse button in the plot area, the structure corresponding to the two dihedral angle values at the cursor position is displayed in the Workspace.

4. When you have finished, close the 2D Plot panel and choose Close from the Project menu.

3.13 MINTA Prediction of Free Energy

MINTA is a powerful tool for estimating free energies from individual conformations or collections of conformations. Many common methods for estimating the free energy of a conformation do so based on a single point in conformation space (i.e., the exact coordinates provided). A key feature of MINTA is that an integration is performed over the normal modes for each conformation in order to accurately estimate the free energy of the local potential minimum as a whole. As with other free energy methods, performing multiple MINTA calculations and taking the appropriate differences among them can yield estimates of binding free energies. Note that while MINTA and MacroModel are tightly coupled, additional licensing is needed to run MINTA.

This exercise uses MINTA to estimate the free energy of the substituted thymine structure based on the results of the conformational search in Section 3.8.1 on page 64.

The MCMM computation contained multiple structures in the output file. The entire set of conformers can be used as input to MINTA, or, to shorten the computation, a subset of the lowest energy structures can be used.

1. Create a new project and import the conformational search output `MCMM-out.mae` into the Project Table, or import the structures from `Minta.mae` from the `QuickTopics` directory, using the directions in Section 3.3.1 on page 31.

2. Select all entries in the Project Table, or just a subset of the lowest energy structures.

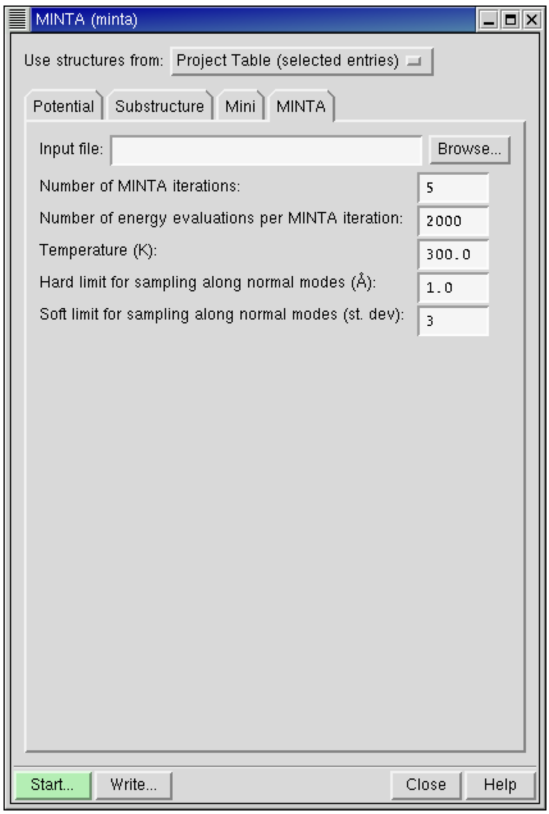


Figure 3.29. The MINTA ***panel showing the*** MINTA ***folder.***

3. Choose MINTA from the MacroModel submenu of the Applications menu.
4. Choose Project Table (selected entries) from the Use structures from option menu (see Figure 3.29 on page 83).
5. In the Potential folder, choose the same force field that you used to perform the conformational search. (The `Minta.mae` file was generated using MMFFs.)
6. Click Start to open the Start dialog box.
7. Choose Append new entries from the Incorporate option menu.
8. Enter `Minta` in the Name text box.
9. Click Start to launch the job.

The MINTA free energy and other information is written at the end of the `.log` file and is included as a set of properties in the Project Table.

10. When you are finished, choose Close from the Project menu to close the project.

3.14 Partition Coefficient Between Two Solvents

MacroModel can estimate the logarithm of the partition coefficient of a solute between two solvents. The GB/SA parameterized solvents available are water, octanol, and chloroform. Multiple solutes can be used as input by selecting entries in the Project Table. The input structures are minimized in each solvent, and the resulting difference in solvation energies is used for the logP calculation.

The octanol-water partition coefficient, logP(o/w), is often used as a measure of molecular hydrophobicity and other environmental parameters. In this exercise, you will run a logP(o/w) calculation from Maestro.

1. Create a new project and import the structure in `LogP.mae` from the `QuickTopics` directory, using the directions in Section 3.3.1 on page 31.
2. Choose Multiple Minimization from the MacroModel submenu of the Applications menu.
3. Choose Workspace (included entries) from the Use structures from option menu.
4. In the Potential folder, choose MMFFs from the Force field option menu and select Octanol from the Solvent option menu.
5. In the Mini folder, enter `5000` in the Maximum iterations text box and enter `0.02` in the Convergence threshold text box.
6. In the Mult folder, select Enable LogP and choose Water from the Secondary solvent option menu (see Figure 3.30).

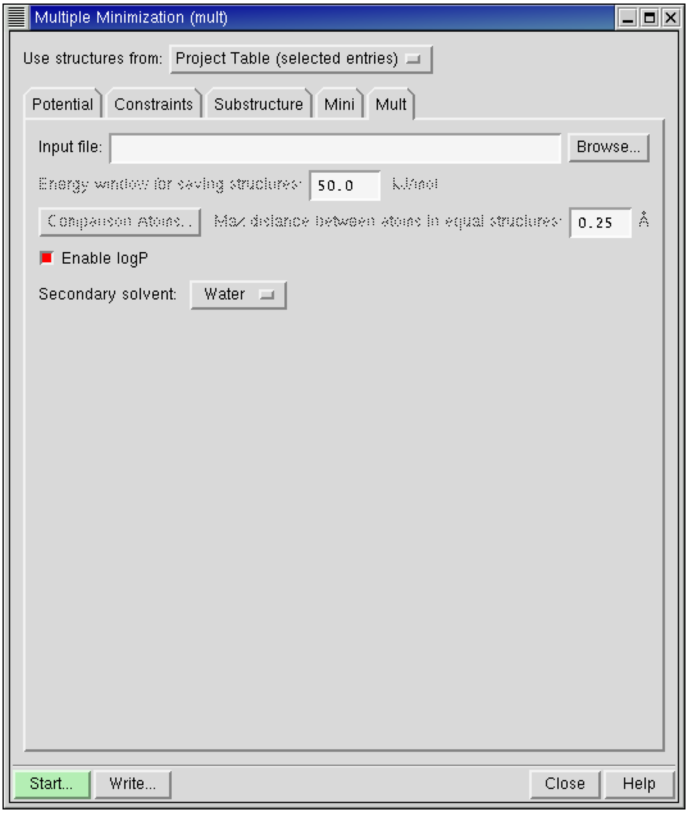


Figure 3.30. The Multiple Minimization ***panel showing the*** Mult ***folder.***

7. Click Start to open the Start dialog box.
8. Choose Append new entries from the Incorporate option menu.
9. Enter `logP` in the Name text box.
10. Click Start to launch the job.

    The Monitor panel is displayed. When the job is finished, the logP(o/w) value is displayed in the monitoring window.
11. When you have finished, choose Close from the Project menu to close the project.

3.15 Analysis of Molecular Structure With XCluster

XCluster is a powerful structural clustering tool that uses molecular similarity as the clustering criterion. XCluster can be run from Maestro, using a set of conformers contained in the Project Facility as input and comparison data selected with Maestro's picking tools. The calculations are run and the results visualized with the XCluster interface, which is automatically started by Maestro.

1. Create a new project and import the structures from `MCMM-out.mae` (see Section 3.8.1) in your working directory, or import the structures from `XCluster.mae` from the `QuickTopics` directory, using the directions in Section 3.3.1 on page 31.
2. In the Project Table, select all 67 structures you just imported.
3. Choose XCluster from the Applications menu.
4. Choose Project Table (selected entries) from the Use structures from option menu (see Figure 3.31).
5. Under Cluster by, select Torsional RMS.

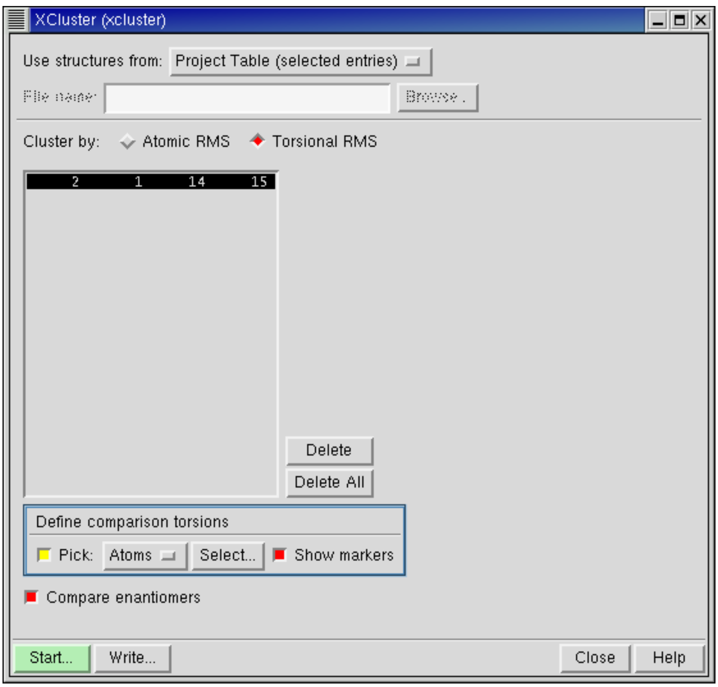


Figure 3.31. The* XCluster *panel.

6. Under Define comparison torsions, choose Atoms from the Pick menu and select atoms in the Workspace for the torsions you want to examine, such as 2-1-14-15.
7. Click Start to open the Start dialog box.
8. Enter `XCluster` in the Name text box.
9. Click Start to launch the job.
10. When the analysis is finished, use the visualization tools by choosing Clustering Statistics, Distance Map, or Clustering Mosaic from the Visualize menu.

Descriptions and examples of the usage of these functions can be found in the *MacroModel XCluster Manual* and in the original literature article.

11. When you have finished, choose Close from the Project menu to close the project.

3.16 Filtering Structures: Sorting and the Plot Facility

It is often useful to identify subsets of a group of structures based on properties such as energy or dihedral angle, which can be stored as properties in the Project Table. Energetic properties are generated from the results of calculations and incorporated automatically into the Project Table. In addition, geometric properties can be created from the Measurements panel and applied to selected entries in the Project Table by selecting Create property for selected entries when making the measurement selection.

Once the properties have been incorporated into the Project Table, there are two independent methods to filter the structures based on a range of the properties. The first method is to use the Sort facility to sort the structures in the Project Table by property value in increasing or decreasing order. The second method is to use the Plot facility and graphically select the structures based on the property values.

3.16.1 Generating Data

This exercise demonstrates how to create properties from measurements for a set of conformers. The properties are automatically added to the Project Table.

1. Create a new project and import the structures in `Filter.mae` from the `QuickTopics` directory, using the directions in Section 3.3.1 on page 31.
2. In the Project Table, select all the entries.
3. Choose an entry and click the In field to include it in the Workspace.
4. Choose Measurements from the Tools menu in the main menu bar to open the Measurements panel.

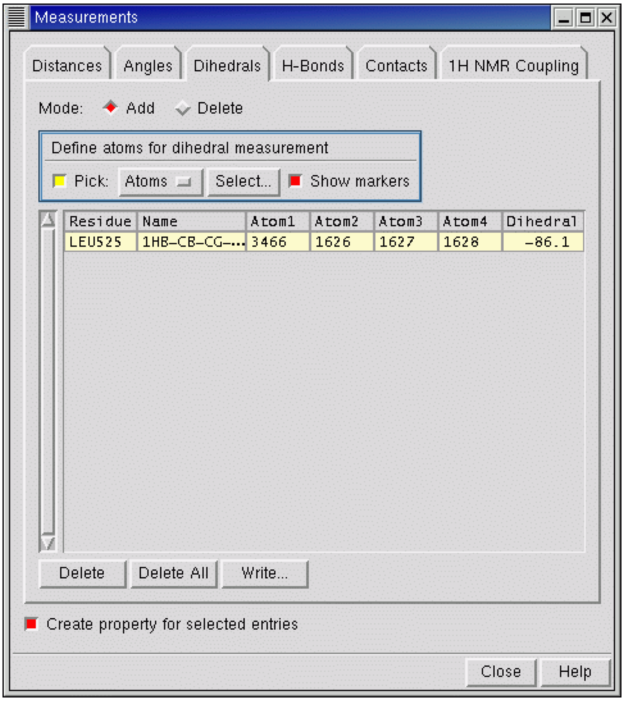


Figure 3.32. The Measurements ***panel showing the*** Dihedrals ***folder.***

5. In the Dihedrals folder under Mode, select Add and Create property for selected entries in the lower left corner of the panel (see Figure 3.32).
6. Choose Atoms or Bonds from the Pick menu and select the four atoms or the central bond that defines the torsion of interest.

   When the torsion is defined, Maestro calculates the dihedral angle for each selected entry and transfers the data to the Project Table as a new property.
7. Close the Measurements panel.

3.16.2 Filtering by Sorting

This exercise demonstrates how to sort the structures based on the dihedral angle generated in the previous section.

1. In the Project Table, select the entries to be sorted.

   You can use shift-click and control-click to select a range of items. Select the entries from the set for which you created properties in the previous section.

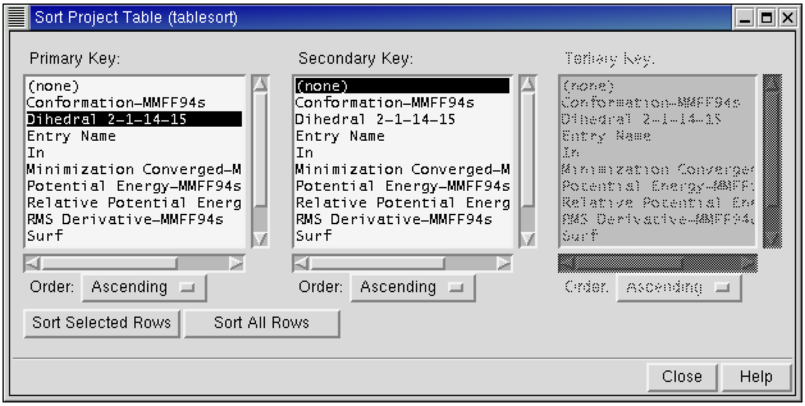


Figure 3.33. The Sort Project Table ***panel.***

2. Click the Sort button in the toolbar.

The Sort Project Table panel opens (see Figure 3.33)

3. In the Primary Key list, select a property such as Dihedral 2-1-14-15.

If you want, you can also choose a secondary key.

4. Choose a sort order from the Order option menu.

5. Click Sort Selected Rows.

The entries in the Project Table are reordered based on the sort criteria.

You can then select a subset of entries with the desired range of properties. These structures can be written to disk or investigated further.

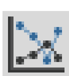
6. When you have finished, close the Sort Project Table panel.

3.16.3 Filtering Using the Plot Facility

This exercise demonstrates how to plot the dihedral angle generated in the previous section and select the desired entries from the plot.

1. In the Project Table, select the structures to be filtered.

2. Click the Plot button in the toolbar to open the Plot XY panel.



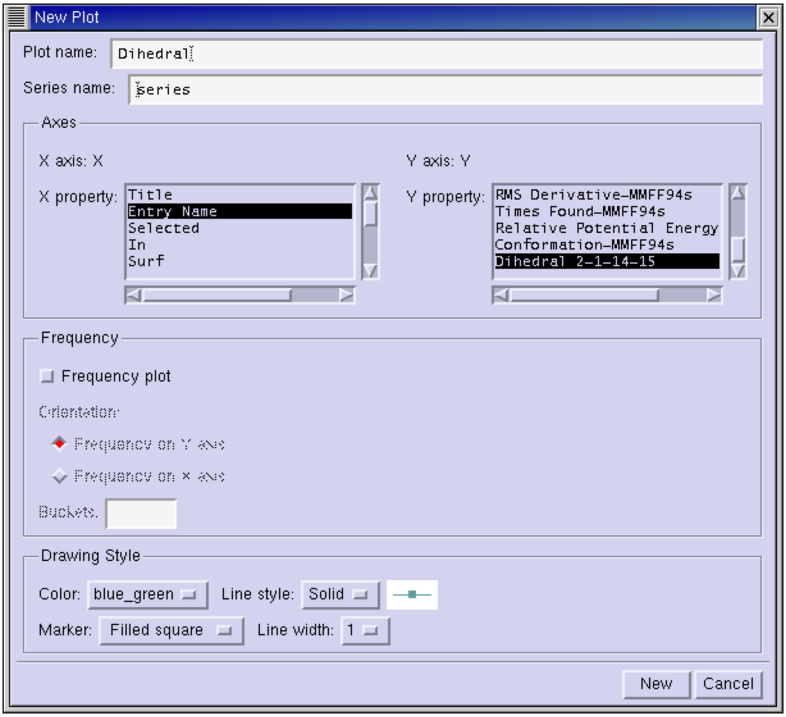


Figure 3.34. The* New Plot *dialog box.

3. Choose New Plot from the Plot menu to open the New Plot dialog box (see Figure 3.34).
4. Enter a name for the plot in the Plot name text box.
5. Under X property, select Entry Name.
6. Under Y property, select the recently defined dihedral angle.
7. Choose your preferred plot and drawing styles.
8. Click New to update the Plot XY panel and plot the data (see Figure 3.35).
9. Click the Select project entries button in the Plot XY toolbar.

10. Click or drag to select a set of points corresponding to a range of dihedral angle values.

    The corresponding entries are selected in the Project Table and can be written out or processed further.

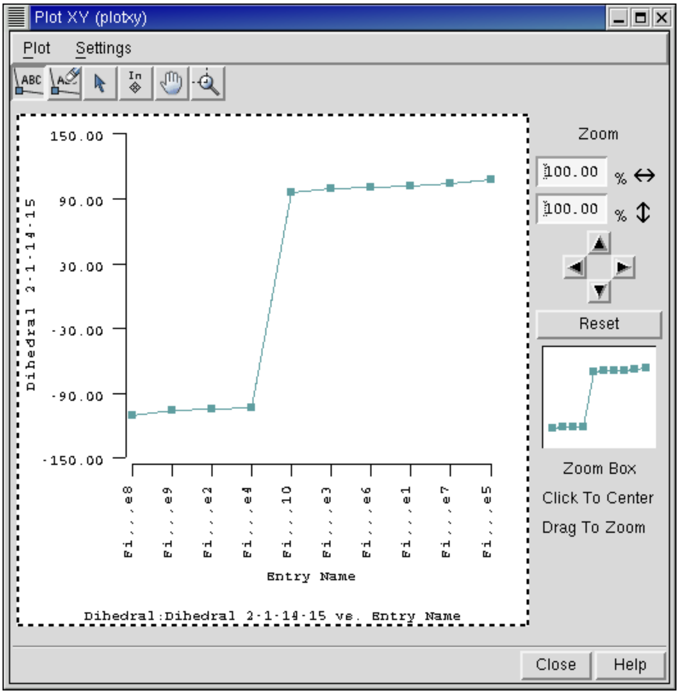


Figure 3.35. The* Plot XY *panel.

In the same way, you can include entries in the Workspace with the Include project entries button.

This concludes the exercises in this Quick Start Guide. For more information on MacroModel functions, see the *MacroModel User Manual* and the *MacroModel Reference Manual*. For more information on the Maestro GUI interface, see the *Maestro User Manual*.

Getting Help

Schrödinger software is distributed with documentation in PDF format. If the documentation is not installed in `$SCHRODINGER/docs` on a computer that you have access to, you should install it or ask your system administrator to install it.

For help installing and setting up licenses for Schrödinger software and installing documentation, see the *Installation Guide*. For information on running jobs, see the *Job Control Guide*.

Maestro has automatic, context-sensitive help (Auto-Help and Balloon Help, or tooltips), and an online help system. To get help, follow the steps below.

- Check the Auto-Help text box, which is located at the foot of the main window. If help is available for the task you are performing, it is automatically displayed there. Auto-Help contains a single line of information. For more detailed information, use the online help.
- If you want information about a GUI element, such as a button or option, there may be Balloon Help for the item. Pause the cursor over the element. If the Balloon Help does not appear, check that Show Balloon Help is selected in the Help menu of the main window. If there is Balloon Help for the element, it appears within a few seconds.
- For information about a panel or the folder that is displayed in a panel, click the Help button in the panel. The Help panel is opened and a relevant help topic is displayed.
- For other information in the online help, open the Help panel and locate the topic by searching or by category. You can open the Help panel by choosing Help from the Help menu on the main menu bar or by pressing CTRL+H.

  To view a list of all available MacroModel–related help topics, choose MacroModel from the Categories menu of the Categories tab. Double-click a topic title to view the topic.

If you do not find the information you need in the Maestro help system, check the following sources:

- *Maestro User Manual*, for detailed information on using Maestro
- *Maestro Command Reference Manual*, for information on Maestro commands
- *MacroModel User Manual*, for detailed information on using MacroModel
- *MacroModel Reference Manual*, for information on MacroModel commands
- Frequently Asked Questions pages, at
  https://www.schrodinger.com/MacroModel_FAQ.html

The manuals are also available in PDF format from the Schrödinger Support Center. Information on additions and corrections to the manuals is available from this web page.

If you have questions that are not answered from any of the above sources, contact Schrödinger using the information below.

E-mail: help@schrodinger.com
USPS: Schrödinger, 1500 SW First Ave. Suite 1180, Portland, OR 97201
Phone: (503) 299-1150
Fax: (503) 299-4532
WWW: http://www.schrodinger.com
FTP: ftp://ftp.schrodinger.com

Generally, e-mail correspondence is best because you can send machine output, if necessary. When sending e-mail messages, please include the following information, most of which can be obtained by entering `$SCHRODINGER/machid` at a command prompt:

- All relevant user input and machine output
- MacroModel purchaser (company, research institution, or individual)
- Primary MacroModel user
- Computer platform type
- Operating system with version number
- MacroModel version number
- Maestro version number
- mmshare version number

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